

Review Article

The Sphenopalatine Ganglion: Anatomy, Pathophysiology, and Therapeutic Targeting in Headache

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The sphenopalatine ganglion (SPG) has attracted the interest of practitioners treating head and face pain for over a century because of its anatomical connections and role in the trigemino-autonomic reflex. In this review, we discuss the anatomy of the SPG, as well as what is known about its role in the pathophysiology of headache disorders, including cluster headache and migraine. We then address various therapies that target the SPG, including intranasal medication delivery, new SPG blocking catheter devices, neurostimulation, chemical neurolysis, and ablation procedures.

Key words: sphenopalatine, pterygopalatine, ganglion, migraine, cluster, neuralgia, headache, neurostimulation, ablation

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INTRODUCTION

The sphenopalatine ganglion (SPG) contains the largest collection of neurons outside the brain.

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It is composed of parasympathetic ganglia predominantly from the greater petrosal nerve and is housed in each unilateral pterygopalatine fossa (PPF). It has also been labeled Meckel's ganglion, the pterygopalatine ganglion (PPG), and the nasal ganglion,¹ but the SPG may be the preferred historical term² and has now long been entrenched in the medical literature. The axons of the SPG innervate the lacrimal gland and the nasal mucosa and they control local blood flow to the area. It has long been implicated in certain head pain conditions and considered a potential therapeutic site for intervention. The SPG mediates blood flow in key areas; its stimulation or blockade may have effects on conditions that depend upon parasympathetic activity.

HISTORICAL CONTEXT

Sluder was recognized as being the first physician to block the SPG via a transnasal approach in 1908.³ His technique involved instilling a 20% cocaine solution into the SPG region. This intervention was followed by the insertion of a 4.5 inch needle through the nostril and placement of a 2% silver nitrate solution, a 0.4% gaseous formaldehyde solution and a 5% phenol solution with a 1% iodine wash. In the 1970s, Ruskin reviewed the remote effects of blocking the SPG and reported efficacy for headaches, facial neuralgias, low back pain, temporomandibular joint dysfunction, and even hiccups.⁴ In addition to local anesthetics, alcohol injected into the PPF also provided some relief.

Devoghel et al were the first to demonstrate benefit in cluster headache (CH) sufferers by blocking the SPG.⁵ In 1982, Barre reported the benefit of an intranasal application using a cotton swab of cocaine as an abortive agent to relieve CH acutely.⁶ Kittrelle demonstrated, in a small study in 1985, benefit with a 4% lidocaine solution equivalent in potency to that utilized with cocaine, suggesting that the effect was related to an anesthetic and not a sympathomimetic effect.⁷ Kudrow⁸ and Maizels et al⁹ also described the successful use of intranasal lidocaine in the acute treatment of migraine. The traditional procedure for SPG blockade involves a supine position with the medication introduced via the patient's nares with a cotton tipped applicator

soaked in an anesthetic solution, later modified by the use of a novel device to deliver topical transnasal analgesic in 2006,¹⁰ which has since been followed by other new devices. In 2009, Tepper et al demonstrated preliminary efficacy of implantation of an electrical stimulator in the SPG in refractory migraine sufferers.¹¹ Other interventional therapies targeting the SPG have also been under investigation and will be described herein.

ANATOMY

The SPG is a triangular, conical, or heart shaped ganglion located under a thin (1-2 mm) layer of mucosa in the PPF, typically on the medial wall.^{10,12} It is suspended from the maxillary nerve via two nerve branches and sits within the PPF, typically located near the lateral insertion of the posterior middle turbinate (Fig. 1).¹²

The SPG has three inputs receiving sensory, parasympathetic and sympathetic projections. The nerves leaving the SPG include the nasopalatine nerve, greater palatine nerve, lesser palatine nerve, posterior, superior and inferior lateral nasal branches, and pharyngeal branch of the maxillary nerve.¹³ There are also delicate orbital branches, which pass directly to the apex of the orbit and eventually the lacrimal gland.^{14,15}

The maxillary nerve passes through the foramen rotundum and traverses the PPF, sending two ganglionic branches to the SPG.¹³ For the most part, these sensory branches pass directly through to the lesser and greater palatine nerves without synapsing.^{13,16} The greater palatine nerve supplies sensation to the bony palate, gingival, and mucosa of the buccal cavity. The lesser palatine nerve supplies sensation to the uvula, tonsils, and soft palate.

The sympathetic fibers that traverse through the PPF do not synapse within the SPG. They arise from the superior cervical ganglion, travelling through the internal carotid plexus and then the deep petrosal nerve, which joins with the greater petrosal nerve to form the nerve of the pterygoid canal (Vidian nerve),¹⁷ before entering the PPF. Sympathetic axons pass through the PPF, and are distributed to the nasal and pharyngeal mucosa predominantly, with some sympathetic fibers reaching

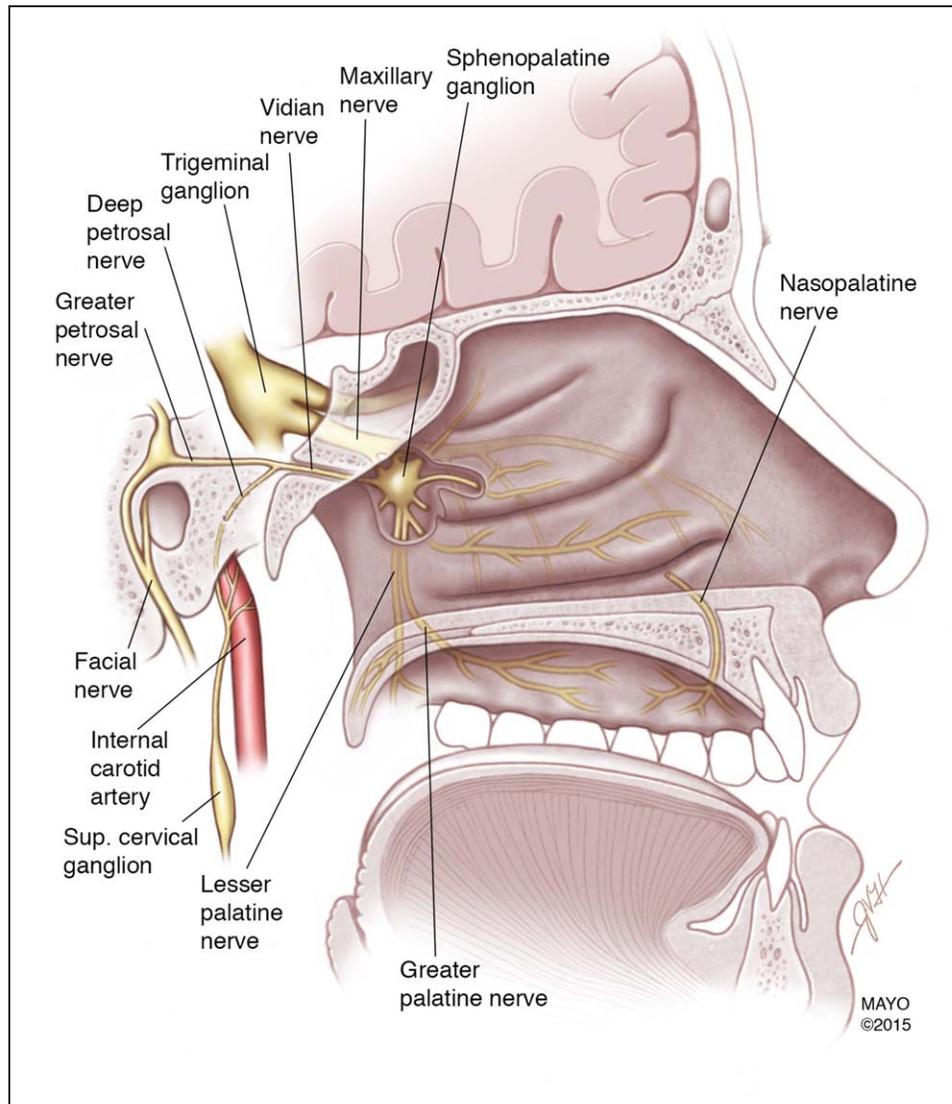


Fig. 1.—Sagittal view drawing through the nasopharynx demonstrates the sphenopalatine ganglion and its direct connections.

the lacrimal gland via orbital branches of the SPG.¹⁵ There may be additional sympathetic input to the PPF, from the external carotid artery plexus (via the maxillary artery plexus).¹⁵

Parasympathetic inputs derive from the superior salivatory nucleus (SSN) in the brainstem. The efferent fibers from this nucleus travel in the nervus intermedius, which is a component of the facial nerve, through the geniculate ganglion, and form the greater petrosal nerve. The greater petrosal nerve then passes through the Vidian nerve to the SPG. Most of these fibers then synapse with postganglionic fibers

which travel with trigeminal nerve branches to provide secretomotor function to the mucous membrane of the nose, soft palate, tonsils, uvula, roof of the mouth, upper lip and gums, upper part of the pharynx, lacrimal gland, and meningeal vessels.^{18,19}

The seventh nerve parasympathetic innervation increases the secretomotor function of nasal-palatal mucosa. The sympathetic innervation is inhibitory to the same elements. The secretomotor production is more watery-mucoid with parasympathetic stimulation, and more viscous-mucoid with sympathetic stimulation.²⁰

PATHOPHYSIOLOGY

The SSN is stimulated by trigeminal afferents, and activates the postganglionic parasympathetic neurons in the SPG. Stimulation of the SPG has also been shown to activate cerebral vasodilatation and increase cerebral blood flow.²¹ SPG activation may result in the release of acetylcholine, vasoactive intestinal peptide and nitric oxide in dural blood vessels. This may increase plasma protein extravasation with resultant neurogenic inflammation and activation of trigeminal nociceptors contributing to pain and triggering headache.^{22,23}

The SPG plays a unique role in headache disorders as the key peripheral structure responsible for the expression of cranial autonomic symptoms, most commonly seen in the trigeminal autonomic cephalalgias (TACs). The TACs are characterized by unilateral headaches that are classically associated with autonomic features, which can be both attributed to parasympathetic activation (lacrimation and rhinorrhea), sympathetic dysfunction (ptosis), or both (miosis).¹⁷ The specific activation of these circuits within the SPG explains the clinical manifestations seen in CH, which is the most common TAC.² SPG blockade is thought to relieve TACs by targeting these specific pathways that are central to headache pathophysiology.²⁴ These autonomic findings are frequently described in migraine as well. The direct connection to the maxillary branch of the trigeminal nerve may also explain why blockade of the SPG may be helpful in trigeminal neuralgia and may contribute to its efficacy in migraine.

Recent insights into CH pathophysiology relate to the mechanism of oxygen as an acute therapy, where the target appears to be the parasympathetic facial/greater superficial petrosal nerve pathway instead of a direct effect on the trigeminal nucleus or trigeminal afferents to the dural vasculature.²⁵ A recent review of oxygen in CH headache suggests it may act as a neuromodulator on neurotransmitter levels and inhibit neurogenic inflammation via deactivation of the trigemino-autonomic reflex arch.²⁶

Sphenopalatine Ganglion Blockade.—SPG blockade has long been employed for headache treatment.²⁷ The most common indication for this procedure in headache practice has been CH, prob-

ably since the SPG has a major role in cranial parasympathetic outflow, raising the notion that it may be involved in CH pathophysiology.²⁸ Reports on the use of cocaine to block the SPG for the treatment of headaches (that were likely CH) date back more than a century.^{3,28} Intranasal lidocaine has been more commonly used to block the SPG, due to its more favorable safety profile, and the risk of addiction associated with cocaine use. SPG blockade has also been used to treat migraine and other headache disorders, with some success.^{8,29–31}

Cluster Headache.—The efficacy of SPG block in the treatment of CH has been examined in a number of studies over the past several decades.^{6,7,28,32–36} The majority of those studies were open and uncontrolled. In an open study, Barre used intranasal application of cocaine to treat acute CH attacks (the majority of which were nitroglycerin-induced) in 11 patients.⁶ Within 2.5 minutes after treatment, head pain decreased by $\geq 80\%$ in 91% of the patients. Cranial autonomic symptoms also improved or resolved rapidly after treatment. Kittrelle et al used a 4% lidocaine solution, dropped intranasally ipsilateral to the pain, to block the SPG in five CH patients for the treatment of nitrate-induced attacks.⁷ Treatment was given within 5–10 minutes after headache onset. Four patients experienced $>75\%$ pain reduction within 3 minutes after treatment. Associated autonomic symptoms also improved or resolved rapidly. The treatment, self-administered by the patients, was also effective for spontaneous CH attacks. In another study, 24 CH patients were given either cocaine 10% or lidocaine 4%, applied to the SPG area using a nasal dropper, for the treatment of acute attacks.³³ Both treatments were similarly effective in relieving pain and autonomic symptoms. Symptomatic relief occurred within 5 minutes or less after treatment. Robbins evaluated the effect of intranasal lidocaine on acute CH attacks in an uncontrolled study of 30 male patients.³² Lidocaine 4% spray was self-administered during attacks. Fifty-four percent of patients experienced mild to moderate relief after treatment, while 46% had no relief, and the treatment was well tolerated.

In a double blind controlled study, Costa et al examined the effect of lidocaine 10% or cocaine 10%, given intranasally and bilaterally using a cotton swab under anterior rhinoscopy, on nitroglycerin-evoked attacks in nine CH patients.³⁴ All patients responded to both drugs, with a significant decrease in pain and autonomic symptoms within 5 minutes, but no difference between the two drugs. Saline administration was not effective, and all treatments were well tolerated. More recently, Felisati et al reported on the results of SPG blocks in 20 patients with refractory chronic CH.³⁵ To block the SPG, the PPF was approached endoscopically through the lateral nasal wall. A mixture of local anesthetics and triamcinolone was injected using a 20 gauge needle. There was a significant, but temporary, improvement of symptoms after treatment in 11 (55%) patients (8 had a complete elimination of attacks for <1 to 24 months, while 3 had partial response, with decreased frequency and intensity of attacks). One patient developed epistaxis after the procedure, and three patients had transient diplopia. In a later study by the same group, SPG blockade was performed on 15 refractory chronic CH patients, using a modified endoscopic technique.³⁶ A combination of local anesthetics (bupivacaine and mepivacaine) and triamcinolone was used for SPG blockade. Eight (54%) patients were attack free for variable periods of time after treatment (1-28 months, with three patients still in remission at the time of result-analysis). One patient had partial symptomatic relief after treatment, while six had no substantial benefit. Two patients had postprocedural severe epistaxis and one had reduced buccal opening that subsequently resolved.

Most recently, an open-label pilot study assessed the efficacy and safety of a single injection of 25-50 units of onabotulinumtoxinA administered to the PPF under general anesthesia with preoperative imaging guidance in 10 patients using either a transnasal (n=9) or percutaneous infrazygomatic (n=1) approach in 10 patients with intractable chronic CH.³⁷ In the intention to treat analysis, CH attack frequency at weeks 3 and 4 were reduced to 11 ± 14 from 18 ± 12 per week at baseline

($P = .038$). Posterior epistaxis requiring nasal packing (n=1) was the only severe adverse effect reported. Other probable treatment related adverse effects included ipsilateral ocular accommodation problems (n=3) and chewing and gaping difficulties (n=1), all resolving within 4 weeks.

Migraine.—There have been a number of studies published over the years on SPG blockade, using intranasal lidocaine for the treatment of migraine, including one case report,³⁸ an uncontrolled study,⁸ and four small, randomized trials.^{9,39-41} In 1999, Maizels published a case report of a 15-year-old boy who had episodic migraine with aura. The patient was instructed to use 0.5 mL of 4% intranasal lidocaine during his aura, and this consistently aborted his migraine headache over a 15 month period.³⁸ After ceasing its use his attacks remained mild or nonexistent after aura, suggesting a prophylactic effect. An uncontrolled study using 0.4 mL of 4% intranasal lidocaine also found it to be helpful in aborting migraine attacks in 12 of 23 (52%) patients, with sustained relief at 24 hours.⁸ Side effects were minimal, including bitter taste, transient ipsilateral nostril and eye burning sensation, and oropharyngeal numbness, which resolved after 20 minutes.

However, controlled studies regarding intranasal lidocaine for migraine have yielded mixed results. The first placebo-controlled study regarding intranasal lidocaine for migraine was published in 1996 by Maizels et al.⁹ The authors enrolled 81 subjects who presented to an urgent care department. Subjects were treated with either 4% solution of intranasal lidocaine or saline. Subjects treated with lidocaine were significantly more likely to experience relief from headache, nausea, and photophobia within 15 minutes of treatment, compared with those who received saline. Unfortunately, treatment benefit was not sustained, with many subjects experiencing headache recurrence, typically within an hour of treatment.

A 1999 randomized, controlled, double-blinded study with an open label follow up evaluated the efficacy of 0.5 mL of 4% intranasal lidocaine, self-administered at home, as acute migraine treatment.³⁹ In the initial double-blinded study portion

that included 131 subjects, intranasal lidocaine was found to be superior to placebo in its ability to abort a migraine attack within 15 minutes of treatment. Headache recurred, however, in 21% of subjects receiving lidocaine. In the 6 month open label phase, the subjects who initially found intranasal lidocaine to be useful continued to experience treatment benefit. Side effects, which were transient and not serious, included bitter taste, nostril burning, and oropharyngeal numbness. Another randomized controlled study found that 1 mL of 4% intranasal lidocaine was not better than placebo in the acute treatment of migraine for patients presenting to the emergency department (ED).⁴⁰

More recently, a 2012 randomized study examined the efficacy of intranasal ketorolac with lidocaine, as compared with lidocaine alone, for the acute treatment of migraine.⁴¹ Though the use of intranasal ketorolac was not intended to directly target the SPG, a treatment effect by the use of lidocaine on the SPG in both treatment arms may have played a role in aborting attacks. The 140 subjects received either 31.5 mg ketorolac tromethamine and 6% lidocaine, or 6% lidocaine alone. Subjects were advised to self-treat within 4 hours of a migraine attack. Although there was no between-group difference in the number of patients experiencing pain freedom at 2 hours (the primary end point), ketorolac with lidocaine was superior to lidocaine alone in a number of other secondary time points. Side effects were minimal, with subjects in both groups experiencing mild nasal discomfort and transient oropharyngeal numbness.

Other Headache Disorders.—A 2014 randomized controlled prospective study from Iran looked at the efficacy of 10% intranasal lidocaine in aborting headache, regardless of type, in patients presenting to the ED.³⁰ Ninety patients with various headache types were included: migraine (n = 18), tension-type (n = 31), post-traumatic (n = 21), or a secondary nontraumatic headache (acute sinusitis, n = 10; brain tumor, n = 3 subjects; acute glaucoma, n = 3; subarachnoid hemorrhage, n = 2; temporal arteritis, n = 1; subdural hematoma, n = 1). Patients were treated with either 1 puff of 10% intranasal lidocaine or saline. Intranasal lidocaine was signifi-

cantly more effective than saline at aborting headache, regardless of type, at 1 minute post-treatment, and this benefit was sustained at 30 minutes.

Cohen et al have published two letters to the editor detailing their experience treating 32 obstetric patients with postdural puncture headache with SPG block.^{31,42} Approximately 69% of their patients found this treatment to be effective, avoiding the need for an epidural blood patch. Chae et al published two cases of post-traumatic headache in which 2% intranasal viscous lidocaine was effective.⁴³ Saberski et al reported a single case of postherpetic trigeminal neuralgia, associated with sinus arrests during pain paroxysms, that was effectively treated with an ipsilateral SPG block using two 10 cm cotton tipped applicators dipped in 20% lidocaine.²⁹ The intranasal lidocaine was effective in providing 30 hours of relief from her pain and sinus pauses, and repeat blocks had the same effect. **Technique.**—A number of techniques have been used in the different CH studies to administer drugs to the SPG area for the purpose of blockade. These included local application of the drug, administering it using a dropper, spraying, and injecting the drug under direct visualization. The technique used in the migraine studies was more uniform, and has been referred to as the method of Barre.^{8,9,38–40} Patients are asked to lie on their back with their heads tilted upwards and their chins toward the ceiling, such that the bridge of the nose is below the level of the throat. The tip of the syringe containing lidocaine is inserted into the nostril, and medication is dispensed over 30 seconds. The patient is asked to lie still with the head in the same position for another 30 seconds, before repeating the procedure on the other side.

Sphenopalatine Ganglion Blocking Catheters.—Intranasal devices are an emerging focus for the development of SPG blockade. Unlike conventional transnasal, infrazygomatic, or transoral approaches, intranasal devices potentially may offer higher tolerability. The currently available intranasal devices include the SphenoCath[®] and Allevio[®] SPG nerve block catheters and the Tx360[®] nasal applicator. The Sphenocath[®] and Allevio[®] catheters are

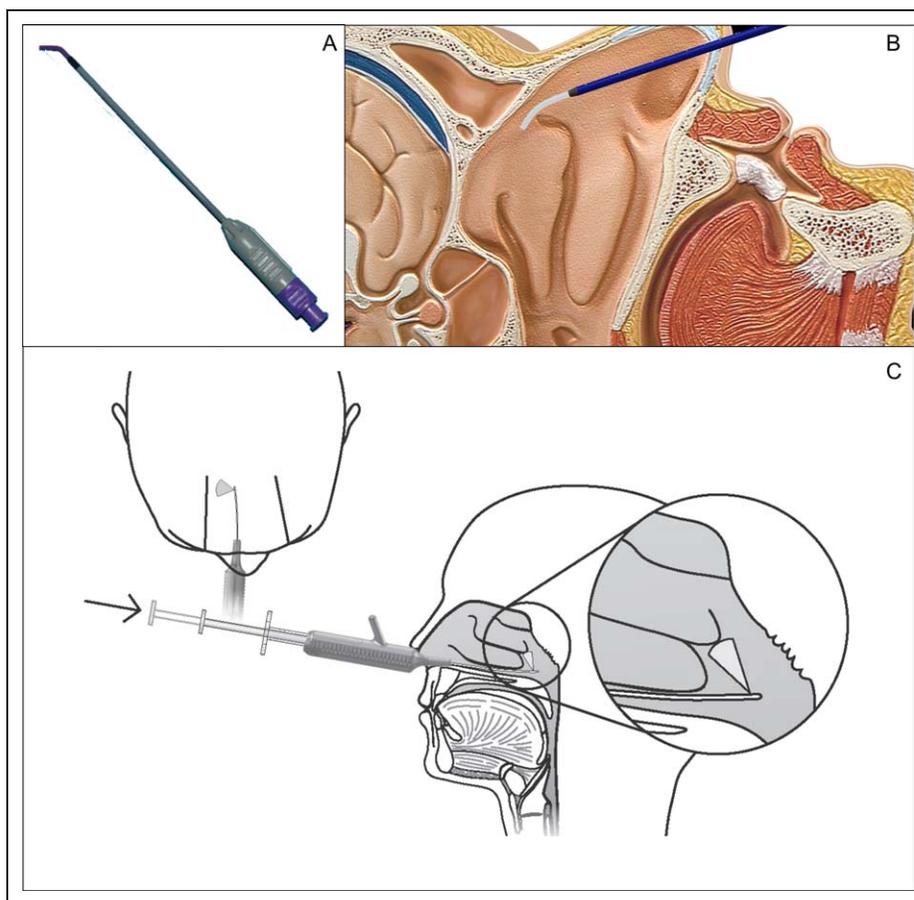


Fig. 2.—Newer sphenopalatine ganglion blocking catheters. (A) Illustrates the Sphenocath[®] nerve block catheter. (B) Illustrates placement of the Allevio[®] SPG catheter superior to the middle turbinate in the sagittal plane. (C) Illustrates the Tx360[®] nasal applicator, including its insertion and placement in the inferior aspect of the nasal cavity and catheter tip destination below the middle nasal turbinate. Images provided courtesy of Dolor Technologies, LLC, Jet Medical, and Tian Medical.

inserted along the anterior nasal passage and placed superior to the middle nasal turbinate. In contrast, the Tx360[®] device is advanced parallel to the bottom of the nasal cavity with the catheter tip positioned below the middle nasal turbinate.

SphenoCath[®] and Allevio[®].—Despite the availability of the SphenoCath[®] and the Allevio[®] catheters, there is a void in the literature regarding their efficacy and tolerability in clinical practice. Both catheters employ the use of a flexible sheath comprising of an inner, extendible catheter with a curved tip (Fig. 2). Blood pressure and heart rate should be checked preprocedure and postprocedure. The patient is placed in a supine position with cervical spine extension. The nares are visualized for potential obstruction that would

impede the procedure, such as a deviated septum or neoplasm. For patient comfort, the nasal passageway can be anesthetized prior to device insertion with a small quantity of 1 to 2% lidocaine via a needleless syringe or atomizer. The sheath is inserted into the nasal passageway superior to the middle turbinate using tactile judgment for proper placement. Alternatively, fluoroscopy may be used to confirm location of the tip of the sheath. Thereafter, the inner catheter is advanced to administer an anesthetic agent, most commonly 1 to 2 mL of 2% lidocaine, to saturate the PPF. Following the application, the device is removed and the procedure is repeated on the opposite side if needed. The patient is maintained in a supine position for 8-10 minutes.

Tx360[®].—Four studies have been reported to utilize the *Tx360*[®] device for SPG blockade. The first is a case series of three patients featuring one patient each with trigeminal neuralgia, chronic migraine, and postherpetic neuralgia.¹⁰ All were administered a combination of 0.5 mL ropivacaine 0.5% and 0.5 mL dexamethasone 2 mg delivered to each nostril. Pain was assessed at 15 and 30 minutes, then at days 1, 7, 14, 21, 28. After 28 days, patients received up to 10 SPG blocks over one year. All three patients had significant pain relief at 15 minutes, and two patients (trigeminal neuralgia and chronic migraine) experienced significant pain relief at day 28. Repetitive blocks over one year showed marked reduction in pain for all patients, and patients were able to remain off additional therapy or medication, suggesting a prophylactic effect.

The second study utilizing *Tx360*[®] was a randomized, double-blind, placebo-controlled trial that evaluated SPG blockade via *Tx360*[®] with 0.3 mL of 0.5% bupivacaine bilaterally vs. 0.3 mL of normal saline bilaterally for acute treatment in the emergency department of anterior or global-based headache.⁴⁴ Classification of headache type was not performed, and 93 patients were enrolled, with 87 patients completing the study. Pain and nausea were rated at 0, 5, and 15 minutes. The primary end point was a 50% reduction of pain and nausea at 15 minutes. A 24 hour phone call was placed for follow-up. There was a trend but no significant difference between the two groups for the primary end point (48.8% in the bupivacaine group versus 41.3% in the saline group). At 24 hours, 72.2% of the bupivacaine group and 47.5% of the saline group were headache free.

Cady et al published two reports of a randomized, double-blind, placebo controlled, parallel-arm pilot study looking at repetitive SPG blocks with *Tx360*[®] as acute treatment for chronic migraine.^{45,46} The study featured SPG blockade via *Tx360*[®] performed twice weekly for 6 weeks, ascertaining for immediate and 6 month pain reduction. Patients randomized to the active arm were given 0.3 mL of 0.5% bupivacaine bilaterally, versus placebo (same volume of saline). Thirty-eight subjects were included, 26 in the active arm and 12 in the placebo

arm. In the group treated with bupivacaine, at 15 minutes, 30 minutes, and 24 hours post-procedure, pain was reduced compared to placebo ($P < 0.001$). While the bupivacaine group had decreased headache days at 1 month and HIT-6 was decreased at 1 month and 6 months post-treatment, the improvement was not significant compared to the saline group. The bupivacaine group was also noted to use less acute medication and had improved quality of life scores up to 6 months post-treatment, but this did not reach significance. The evidence suggests a potential for acute benefit and for further improvement with repetitive SPG blocks over time. How often blocks should be done, however, is unclear, and though 3 of the 4 studies used bupivacaine, it is unclear if this is the ideal drug to be employed.

In contrast to the SphenoCath[®] and Allevio[®] catheters, SPG blockade with the *Tx360*[®] device is administered with the patient seated and upright.⁴⁴ Blood pressure and heart rate are recorded pre and postprocedure. For patient comfort, both nasal cavities can be anesthetized prior to the procedure; a small amount of either 2% lidocaine or 0.5% bupivacaine can be given via syringe or applied with a cotton-tip applicator into the nostril on each side. Once this is completed, the device can be placed into one nostril and the catheter should be advanced (Fig. 2). To each nostril 0.3 ml of 0.5% bupivacaine can be injected via syringe attached to the catheter. The catheter should be withdrawn and the device taken out of the nostril and placed into the opposite nostril to repeat the procedure. A total of 0.6 mL of 0.5% bupivacaine is given to the patient at the end of the procedure.

Adverse Effects.—Side effects are similar for all three devices used. Patients may feel a sensation of mild discomfort during the procedure. Patients may also notice burning during the procedure, and the medication may lead to an unpleasant taste. There may be numbness in the back of the throat after the procedure as some of the medication may be swallowed. Patients should be instructed to avoid eating or drinking until the numbness passes to avoid choking. Other potential side effects are lowered blood pressure, nausea, and epistaxis. An

unpleasant taste may also be experienced if some of the anesthetic reaches the oropharynx, and in clinical studies this may limit blinding. Studies utilizing the Tx360[®] recommend having the patient suck on a mint candy during the procedure to minimize this adverse effect.^{45,46}

Sphenopalatine Ganglion Neurostimulation.—*Mechanism.*—SPG stimulation is thought to work by neuromodulation (alteration of nerve activity via delivery of targeted electrical stimulation or chemical agents) and is an area of active investigation as an emerging treatment, specifically for refractory chronic CH. SPG neuromodulation may either be pro-nociceptive or anti-nociceptive. In a pronociceptive setting, SPG stimulation can provoke cluster-like headache attacks.⁴⁷ The effect of SPG stimulation on the modulation of pain pathways is thought to be a result of the frequency of the stimulation.^{47,48} Low frequency stimulation (10-20 Hz) may result in intra- and extracranial vasodilation and plasma protein extravasation which may, through a cascade of events, result in neurogenic inflammation and subsequently pain.^{48,49} SPG stimulation with a mean frequency of 120.4 ± 15.5 Hz (range: 80–180), mean pulse width of 389.7 ± 75.4 μ s (range: 244–480), and mean intensity of 1.6 ± 0.8 mA (range: 0.6–3.9) during full stimulation, contrasting with 0.5 ± 0.3 mA (range: 0.1–1.4) during subperception stimulation, may be effective for both acute and preventive treatment of refractory chronic CH and may improve quality of life in these patients.²⁴

Cluster Headache.—In a multi-center, double-blind, placebo-controlled study (Pathway CH-1) of 43 patients with refractory chronic CH, 68% experienced clinically significant improvements with pain relief or freedom in more than 50% of attack treatments and/or 50% reduction in attack frequency.²⁴ In a long term (14 months-3 years) follow-up study, data on the effectiveness of SPG stimulation in CH was recorded in 26 out of 33 patients. The average number of attacks treated per patient was 197 (range 1-1489). A total of 5132 attacks were treated (22% mild initial pain, 47% moderate, 22% severe, 9% very severe). Nearly two-thirds (65%) of these attacks were treated effectively. The average stimula-

tion duration was 12.9 minutes. The authors concluded that two-thirds of more than 5,000 cluster attacks evaluated during the long-term follow-up were effectively and safely treated.⁵⁰ In an open label registry of SPG stimulation therapy, 18 patients completed follow-up through 6 months. The average baseline attack frequency was 28.4 attacks/week (range 0-70), and the average attack frequency at 6 months was 17.3 attacks/week (range 0-70), a 40% reduction. Two-thirds of patients were responders, of whom 67% were acute responders, 75% were attack frequency responders, and 42% were both acute and frequency responders.⁵¹ A recent review suggested that SPG stimulation may be a cost-effective treatment modality for chronic CH patients in comparison to medical management.⁵²

Migraine.—SPG stimulation has been reported in a study including two patients with episodic migraine and eight patients with chronic migraine complicated by medication overuse. The results were variable, including two patients with complete attack resolution, three patients with partial reduction of headache attacks and five patients with no response. Lead placement and diagnoses (particularly medication overuse) were thought to be the factors that may impact treatment success.¹¹ As this study, new technology for SPG stimulation has been developed and successfully utilized.²⁴

Other Headache Disorders.—Our knowledge on the use and evidence for SPG stimulation in other headache disorders is limited. There are reports of pain reduction with neurostimulation of other peripheral nerves (occipital, supraorbital/supratrochlear, vagus) in several types of headache disorders including hemicrania continua, chronic migraine, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).⁵³ Investigations for SPG stimulation in other headache disorders may be warranted, particularly for the other TACs.

Adverse Effects.—The adverse event profile is highly related to the method of placement and type of SPG stimulator. In the Pathway CH-1 trial, 5/32 (15.6%) patients experienced device or procedure related serious adverse effects, including lead

misplacement or migration requiring revision ($n = 3$) or explantation ($n = 2$). Most patients (81%) experienced sensory disturbances, the majority of which resolved over weeks to months. Less common adverse events include tooth sensitivity, postoperative swelling and pain, trismus, headache, dry eyes, hematoma, paresis, and infection resolving with antibiotics ($n = 2$).²⁴

Clinical Use.—Lambru and Matharu suggest that clinical use of peripheral nerve stimulation is limited by lack of proper controlled data and should only be considered in patients with primary chronic headache disorders who have failed therapies recommended by international guidelines.⁵⁴ An expert consensus on patient selection including inclusion and exclusion criteria as well as standards of care for stimulation of the SPG in patients with intractable CH has been recently published.²³ However, more studies investigating SPG stimulation are underway at the time of this writing.

Other Procedures Targeting the Sphenopalatine Ganglion.—**Chemical Neurolysis.**—SPG neurolysis dates back over a century with Sluder's use of destructive substances to treat "neuralgia" resistant to repetitive local anesthesia with cocaine.^{3,55,56} Alcohol, phenol, and glycerol are the most common contemporary substances utilized for neurolysis. No randomized, blinded placebo-controlled trials have been conducted using SPG neurolysis.

A retrospective review of eight cases of recurring head and face pain diagnosed as Sluder's neuralgia was presented by Puig et al.⁵⁷ Those responding to local anesthetics first received intranasal transmucosal application of 88% phenol for 15-30 seconds, repeated 2 to 5 times, using topical nasal xylocaine spray between treatments as necessary. This procedure was repeated on average 13 times per patient (range 3-40) with reported mean pain relief of 90% (range 50-100%), for a mean of 9.5 months (range 1 to 29), and a pattern of gradually progressive pain decrease with consequent applications. A similar protocol was used successfully in a three patient case series.⁵⁸

Varghese and Koshy presented a review of 22 patients with head and neck tumors and inadequate pain control with medications including opioids.⁵⁹

All the patients had pain relief with a local anesthetic test, followed by endoscopically guided intranasal SPG block with 6% phenol, resulting in immediate pain relief in 77%, partial pain relief in 5% and inadequate relief in 22%. One month later all patients still had decreased and more manageable pain. In a retrospective study by Kastler et al alcohol was used for SPG neurolysis in 42 patients with various refractory facial pain syndromes.⁶⁰ The majority of the 58 procedures were performed utilizing infrazygomatic approach under CT guidance with the administration of 0.5 mL of lidocaine followed by 1 mL of absolute alcohol. A $\geq 50\%$ decrease in pain for ≥ 1 month was achieved in 67.2%, lasting for a mean of 10.3 months (range 1-48) but with a 72% recurrence rate. A suprazygomatic approach for SPG neurolysis with alcohol was utilized in the treatment of 120 CH sufferers with a success rate reported above 85% in a retrospective analysis.⁵

Complications of SPG chemical neurolysis include epistaxis, cheek hematoma, scarring in the area of application and palatal paresthesias of variable duration. Inadvertent application of phenol to the facial skin may cause a cosmetic defect; therefore, dripping from the swab should be prevented by squeezing phenol-dipped cotton tip between the fingers. The neurolytic dose may be too small to cause a systemic effect.

Radiofrequency Thermoablation and Pulsed Radiofrequency.—Radiofrequency thermal ablation (RFTA) is a modality of local tissue destruction with heat generated by friction of ions and charged molecules oscillating under the action of high frequency (AM band radio frequency 300-500 KHz) alternating electrical current. The current is conducted between a special RFTA needle and a grounding electrode. The RFTA needle is electrically isolated with only 5-15 mm of the needle tip exposed to the current, producing a high-density electrical field. The grounding electrode has a wide area of contact with the skin with such low energy concentration per unit of the surface that it cannot produce any biologically sensible effects. Temperatures $>45^{\circ}\text{C}$ produce thermocoagulation with local hemorrhage and loss of myelinated fibers. Heating

the needle tip to 80°C for 60 to 90 seconds produces reliable RFTA 8-10 mm in diameter around the non-isolated needle tip. Blood vessels located closely to the RFTA needle may increase dissipation of the thermal energy compromising the effectiveness of RFTA.^{61,62}

Another type of radiofrequency application is called pulsed radiofrequency (PRF). Commonly, the PRF uses 300-500 KHz alternating 45 Volt electrical current in 2 Hz cycles of short (20 ms) duration pulse spaced by off periods (480 ms). The procedure lasts for a total of 2 to 8 minutes. The controlled needle temperature does not exceed 40-42°C and should not lead to thermal coagulation of local tissue. The mechanisms of the analgesic action of PRF have not been completely understood, though increase in c-Fos expression in the dorsal horn,^{63,64} increased expression of activating transcription factor 3,⁶⁵ reversible ultrastructural changes in the peripheral nerve or the dorsal root ganglion^{62,66-69} and other changes have been reported. Though PRF is widely utilized in Europe, it is classified as “experimental and investigational” by insurance companies in the US, which limits its use.

The contraindications for a radiofrequency procedure include uncontrolled coagulopathies, local or systemic infection, an inability to maintain positioning without movements, and an inability to obtain procedural consent. Though no clear evidence to support this practice, many practitioners consider a lack of response to SPG blockade with local anesthetic a relative contraindication, similar to chemical neurolysis. A significant change in the local anatomy due to trauma or surgery may also preclude safe execution of the procedure. In patients with an implanted cardiac pacemaker or defibrillator, precautions are required for potential device interference which may include a preprocedure cardiac assessment for safety, close cardiac monitoring and the availability of an external pacing and defibrillation equipment, particularly in patients who are pacemaker dependent.⁷⁰

Procedural Considerations.—There are several interventional approaches to reach the SPG, with intranasal, infrazygomatic, and suprazygomatic

routes most commonly utilized. C-arm fluoroscopy is necessary to verify correct needle tip positioning for an accurate and safe injection performance. Yang and Oraee published a modified safe intranasal SPG block approach.⁷¹ Their technique featured intranasal application of local anesthesia and sterilization followed by the use of a 26-gauge, 5-inch spinal needle with the sheath cut and an exposed needle tip bent and then lubricated prior to advancement into the anesthetized nasal meatus and advanced until the tip of the sheath reaches the posterolateral wall of the nasopharynx. Contrast can be administered to confirm placement in the PPF.⁷¹

In the infrazygomatic approach, local anesthesia infiltration is performed inferior to the posterior zygoma, superior to the mandibular notch, and posterior to the coronoid process, followed by the introduction of an angiocatheter in the direction of the SPG. An insulated radiofrequency thermocoagulation needle can then be introduced through the angiocatheter and steered carefully under fluoroscopic control on lateral and antero-posterior views to the location of the PPF. Precautions should be taken not to penetrate nasal, orbital or maxillary sinus walls, which can cause significant bleeding. The suprazygomatic SPG block is a modified infrazygomatic block with the needle entry point above the zygoma.⁵

Correct needle positioning is verified with sensory stimulation performed at 50 Hz using 0.5 to 1 Volts. Stimulation of the SPG typically produces paresthesias at the root of the nose. Stimulation of the greater and lesser palatine nerves produces paresthesias in the hard palate and the needle should be relocated slightly more cephalad and medially. Maxillary nerve stimulation leads to upper teeth paresthesias and the needle should be repositioned caudally and medially.⁷² Motor stimulation at 2 Hz and 2 Volts should not cause muscular contractions. After verification of the needle tip position 2-3 mL of local anesthetic is injected and RFTA can be performed.⁷³

Complications are mostly related to the needle insertion and may include infection, epistaxis or internal bleeding, damage to the maxillary artery

and nerve and its branches (greater and lesser petrosal nerves), hemodynamic instability, numbness or dysesthesia of the upper teeth, hard palate, or pharynx, decrease in lacrimation and nasal mucus production.⁷⁴⁻⁷⁶ SPG RFTA can also cause reflex sinus bradycardia and close monitoring of vital signs is essential for early diagnosis of this complication.⁷⁷ As described earlier, a successful SPG blockade for the painful exacerbations of post-herpetic trigeminal neuralgia was also shown to resolve recurrent episodes of bradycardia due to sinus pauses.²⁹

Other Evidence.—A retrospective study evaluated the PRF of SPG through an infrazygomatic approach under fluoroscopic guidance in 27 patients with head and face pain. After sensory and motor stimulation to exclude an incorrect position of the needle, PRF at 42°C was performed for four cycles at 120 seconds each. Pain relief was complete in 35% of the patients, was mild to moderate in 42% and none in 23%.⁷⁸ Data on 30 patients with chronic head and face pain were collected in a mixed retrospective and prospective descriptive study. Pain duration was from 7 months to 2 years and 87% of patients had previous face and/or head surgery. All the patients had positive responses to diagnostic and steroid SPG blocks, were subsequently treated with PRF and followed from 4 to 52 months. The PRF was performed through a fluoroscopically guided infra-zygomatic approach with a 5 mm active tip needle at 42°C during 2 cycles of 120 seconds each. Repeat SPG PRF was performed on 20% of the patients. Pain relief was complete in 21%, mild to moderate relief in 65% and no relief in 14%, and there were no serious adverse effects.⁷⁹ A retrospective study described 15 patients with facial pain or headache who underwent SPG RFTA with two cycles at 80°C for 60 seconds in one sitting. Patients had one to 4 procedures performed with 60% of them having almost complete pain relief, while others had pain relief for ≤ 3 weeks or no relief at all.⁸⁰

A number of small case series have described RFTA and PRF of the SPG in CH.^{81,82} Larger series include a description of 13 episodic and 3 chronic medically intractable CH patients who had

a CT-guided SPG PRF with a mean follow up of 17.0 ± 5.5 months (range 12-30). Retrospective analysis showed that within an average of 6.3 ± 6.0 days following the treatment 85% of episodic CH patients and 33% of chronic CH patients had complete headache relief, though 15% of episodic and 66% of chronic CH patients had no pain relief. There were no reported side effects or complications.⁸³ The long term effect of SPG PRF was retrospectively evaluated in 11 patients with refractory CH over a mean follow-up period of 69.8 ± 12.6 months.⁸⁴ PRF pulse of 20 ms (2 Hz) at 45 Volts was applied at 42°C for 4 minutes, with 72.7% experiencing good to complete pain relief. Complications included one patient with epistaxis and one patient with transient paranasal-palatal numbness. Fifty-six patients with intractable episodic CH and 10 patients with chronic CH with mean follow-up over 2 years were treated by infra-zygomatic SPG RFTA. In the episodic CH group 60.7% had complete, 25% partial, and 14.3% no pain relief, while in the chronic CH group 30% had complete, 30% partial and 40% no pain relief. Epistaxis was observed in eight patients, a cheek hematoma in 11, a partial RFTA lesion of the maxillary nerve in 4, and 3 months long hypoesthesia of the palate in nine patients.⁷⁵ Fifteen patients with intractable chronic CH experiencing temporary pain relief with SPG blockade underwent infra-zygomatic RFTA (2 lesions at 80°C for 60 seconds) under fluoroscopic guidance and were reassessed longitudinally. The mean attack intensity and frequency diminished over an 18-month period. Twenty percent developed improvement only several weeks after RFTA and 46.7% of the chronic CH patients remitted to an episodic CH pattern over 18 months. Twenty percent remained pain-free and off medications at 18 months. Seven patients reported temporary paresthesias in the upper gums and cheek with complete resolution within 3-6 weeks and one patient had a small spot of permanent anesthesia on the cheek.⁷²

Studies on these interventional modalities targeting the SPG are summarized in Table 1. They suggest that RFTA and PRF may be effective for medically intractable headache disorders, though no

Table 1.—Summary of Sphenopalatine Ganglion Pulsed Radiofrequency and Radiofrequency Thermal Ablation Studies

Authors	Year	Diagnosis	Modality	Number of Patients	Pain Relief
Salar et al ⁷⁴	1987	Sphenopalatine neuralgia	RFTA	7	100% complete for 6-28 months
Sanders et al ⁷⁵	1997	Cluster headache (mean FU for 24-29 months)	RFTA: 70°C for 60 seconds	66	ECH: 60.7% complete, 14.3% none CCH: 30% complete, 40% none
Shah et al ⁸⁵	2004	Post-traumatic headache	PRF: 20 ms pulse at 2 Hz, 42°C, 3 cycles of 120 seconds	1	HA free for 19 months after bilateral SPG PRF
Bayer et al ⁷⁹	2005	Chronic head and face pain	PRF: 42°C, 2 cycles of 120 seconds bilaterally	30	21% complete 65% mild, moderate
Narouze et al ⁷²	2009	Intractable chronic cluster headache	RFTA: 80°C for 60 seconds, 2 lesions followed by triamcinolone 5 mg	15	Mean decrease in HA attacks by 2/3 after the RFTA and 1/2 by 18 months
Chua et al ⁸¹	2011	Chronic cluster headache for >10 years	PRF: 45 V, 10 ms pulse at 4 Hz, 42°C, 6 minutes	3	2 HA free at 4 months 1 with no improvement
Oomen et al ⁸⁰	2012	Face and head pain	RFTA: 80°C, 2 lesions for 60 seconds	15	60% had ≥90% relief 40% had poor results
Van Bets et al ⁸⁴	2014	Refractory cluster headache	PRF: 20 ms pulse at 2 Hz, 45 V, 42°C, 4 minutes, or RFTA	11	8 complete or good (PRF) 1 good for 11 months (PRF) 1 none (PRF or RFTA) 1 none with PRF, good with RFTA
Elahi et al ⁸⁶	2014	Hemifacial pain after cavernous sinus meningioma resection	RFTA: 80°C for 90 seconds	1	Significant for 12 months
Akbas et al ⁷⁸	2014	Various intractable chronic facial pain syndromes	PRF: 42°C, 4 cycles of 120 seconds (bilateral in 11% of patients)	27	35% complete 42% mild to moderate 23% none
Fang et al ⁸³	2015	Refractory cluster headache (mean FU 17 ± 5.5 months)	PRF: 20 ms pulse at 2 Hz, 42°C, 3 cycles of 120 seconds	16	11/13 ECH complete 2/13 ECH no relief 1/3 CCH complete 2/3 CCH no relief
Bendersky et al ⁸²	2015	Chronic refractory cluster headache (PRF followed by RFTA)	PRF: 20 ms pulse at 2 Hz, 45 V, 42°C, 3 cycles of 120 seconds RFTA: 2 lesions at 80°C for 90 seconds	3	One patient with 1 month relief and two patients no relief after PRF All three patients had complete relief after RFTA

CCH = chronic cluster headache; ECH = episodic cluster headache; FU = follow up; HA = headache; PRF = pulsed radiofrequency; RFTA = radiofrequency thermoablation.

Table 2.—Level of Evidence Summary for Therapies Targeting the Sphenopalatine Ganglion

Therapy	Headache Disorder	Highest Level of Evidence
Intranasal lidocaine; lidocaine + ketorolac	Migraine	Randomized, double blind, controlled studies ^{9,39–41}
Intranasal lidocaine or cocaine	Cluster	Small randomized, double blind, controlled study ³⁴
Acute blockade using bupivacaine with Tx360 [®] single use	Acute headache	Randomized, double blind, controlled study (negative for primary endpoint, positive for secondary endpoints) ⁴⁴
Repetitive blockade with Tx360 [®]	Chronic migraine	Randomized, double blind, controlled study demonstrating significant acute relief and modest benefits in sustained pain and disability reduction ^{45,46}
Neurostimulation	Migraine	Open label ¹¹
	Cluster	Randomized, double blind, controlled study ²⁴
Radiofrequency thermal ablation	Cluster	Retrospective case series*
Pulsed radiofrequency	Cluster	Retrospective case series*

*See Table 1.

prospective, randomized trials on SPG chemical neurolysis or RF lesioning have been performed.

CONCLUSIONS

Based on our understanding of anatomy and pathophysiology, the SPG is a reasonable target for the treatment of medically intractable headache disorders, particularly CH. The level of evidence is summarized on Table 2. Published data indicate efficacy of SPG blockade for CH and to a degree for migraine, though the data are not robust. Studies utilizing newer catheters suggest some acute and long term benefits but require a dosing frequency that may be cumbersome in clinical practice. Overall, SPG blockade appears to be safe and well tolerated. The optimal lidocaine dose, the potential benefit of combination of local anesthetics, and the role of corticosteroids in this setting, remain to be determined. In addition, the optimal technique of drug administration for SPG blockade is currently undetermined. SPG neurostimulation appears to be a promising therapy with emerging evidence, particularly in the treatment of medically intractable CH. Other therapies targeting the SPG including chemical neurolysis, RFTA, and PRF have a number of anecdotal reports suggesting efficacy and safety particularly for CH, but no prospective, randomized studies have been performed.

Future research is needed to address these unanswered questions. Practically, it is not clear when in the therapeutic hierarchy the clinician who is treating headache should resort to therapies targeting the SPG. Intranasal lidocaine may be indicated for the acute treatment of CH or migraine when other more evidence based therapies fail, are contraindicated, or not tolerated. Newer catheter-based SPG blocking devices show some efficacy and safety in small studies, but implementation in clinical practice may be challenging. Emerging evidence suggests SPG neurostimulation may be appropriate for medically intractable CH, or if other therapies are contraindicated or not tolerated. Direct comparisons are not available to judge the adverse effect profile for SPG versus occipital nerve stimulation, where lead migration and infection may both be common adverse effects.^{87–98} There is no high quality evidence for other interventions targeting the SPG and such therapies should be reserved for when all other interventions fail or are not feasible.

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