

Is the SPG stimulation useful for the treatment of cluster headache?

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Editorial

Cluster headache is a highly debilitating disorder, characterized by bouts of pain, which are amongst the most severe described in humans.¹ Approximately 10 to 15% of patients affected by cluster headache develop a chronic cluster headache. Chronic cluster is characterized by attacks that occur without remission or with remission lasting less than one month during at least a year. Patients with cluster headaches, lack a choice of therapeutic options and in addition, 10% to 20% present attacks that are refractory to the therapy.² The most effective treatment for cluster attacks is subcutaneous triptan injections and a high percentage of patients respond also to inhaled high flow oxygen; however, a vast proportion of patients remain severely disabled.

Abortive therapy, given the short duration of cluster attacks, is challenging, therefore patients are in most cases provided with preventative treatments such as verapamil, divalproex sodium, or topiramate. Nevertheless, these preventative medications can have important side effects, even though patients show a higher tolerance than in other headaches³. Due to the difficulties involved in the existing treatments, patients and clinicians continue to focus on finding new approaches to improve the treatment of this disorder.

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. In cluster headache, postganglionic parasympathetic fibers from the SPG which innervate the cerebral and meningeal blood vessels 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.^{4,5}

SPG has been a target to treat headaches in the last century.⁶ Sluder was the first to use cocaine and alcohol in order to reduce the activity of the SPG with the purpose of treating headache disorders. A series of different interventions on the SPG has been used over time with a view to treating cluster headache. Some of these interventions include applications of substances such as alcohol, lidocaine or corticosteroids and also surgical interventions trying to damage the ganglion (ganglionectomy, cryosurgery, stereotactic radiosurgery). Neurostimulation is the newest approach to SPG intervention.⁷

The problem with some of these interventions is that the duration is limited in time and in some occasions it is necessary to repeat the procedure. On the other hand, RF lesioning or nerve resection therapies, can be beneficial at first but are irreversible procedures. For these reasons, the use of neurostimulation provides a method of acting on the neural pathways avoiding permanent damage to neural tissue.

After the first report in a patient,⁸ and a proof of concept trial in six patients with chronic cluster,⁹ a randomized, sham-controlled study

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was designed. In this study, 32 patients with chronic cluster headache were included in order to know the efficacy of SPG stimulation for the acute treatment of cluster headache.¹⁰ Patients were implanted a SPG neurostimulator in their maxilla through a buccal incision. The lead of the neurostimulator was placed in the pterygopalatine fossa, in the proximity of the SPG. The receptor of the neurostimulator was located below the cheek and patients could activate it on demand through an external handheld remote controller. Instructions were provided to these patients to apply stimulation to moderate or severe cluster pain for up to 15 minutes. 28 out of the total number of patients (32), completed the randomized experimental period. Pain relief was achieved in 67.1% of full stimulation-treated attacks at 15 minutes following the start of stimulation, compared to 7.4% of sham-treated attacks ($p<0.0001$). Although the study was designed for treatment of acute attacks, the stimulation produced also a reduction of attack frequency of 50% at a minimum in 43% of patients. In total, a reduction in the frequency of the attacks of 88% was achieved. 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 to baseline), or both. As a consequence of this significant clinical improvement 64% of the patients improved their disability related with headache and 75% found their quality of life improved significantly.

In this study, most adverse events were due to the implantation procedure; the majority of these events were reduction in or loss of sensation in the maxillary nerve. The intensity of the adverse events was mild in most cases and the majority were resolved within three months of the implant procedure.

Long-term observations about the results of SPG show that the majority of patients showed improvements in headache disability, and SPG stimulation was found useful for treating their headaches. In a population of 33 medically refractory chronic cluster headache patients followed for 24months while receiving on-demand, acute SPG stimulation, it was effective for both acute attack pain relief and attack frequency reductions resulting in clinically significant

improvements. At 24 months, 45% of patients were acute responders, 33% were frequency responders, and six of these experienced both types of response; a long-term overall responder rate of 61% was seen. In addition, 65% of SPG stimulation responders experienced a very strong $\geq 75\%$ response to therapy at 24months. 60% reduced, stopped, or remained off all preventive medications.¹¹

In summary, SPG stimulation is a minimally invasive technique that could be a good alternative in chronic cluster refractory patients. It is effective acute and prophylactically. In the long-term studies, the side effects of the procedure are low and decreasing with the time, while its effectiveness remains. In the future, this approach could be also an alternative in patients with episodic forms with no response to preventive treatments and with contraindication or bad tolerability to acute treatments.

SPG stimulation also could be a reasonable option to consider also in migraine and other trigeminal autonomic cephalgias but further studies in this direction are necessary.

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Conflicts of interest

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