The Treatment of Medically Intractable Trigeminal Autonomic Cephalalgia With Supraorbital/Supratrochlear Stimulation: A Retrospective Case Series

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Introduction: This is a retrospective case series of five patients with intractable trigeminal autonomic cephalalgia (TAC) who were implanted with a supraorbital/supratrochlear neuromodulation system.

Objectives: The aim of this Institutional Review Board–approved study was to investigate the percentage of pain relief, treatment response, pain level, work status, medication intake, implantation technique, lead placement, programming information, and device use.

Results: Trial stimulation led to implantation of all five patients. All patients reported improvement in their functional status in regard to activities of daily living. The device was revised in two patients due to skin erosion. It was later reimplanted in both patients due to worsening of symptoms, again with good pain relief. The device was explanted in two other patients because of the need to perform a magnetic resonance imaging or implant an automatic implantable cardioverter defibrillator. The follow-up of the patients ranged between 18 months and 36 months, with a mean of 25.2 months. There was no change in work status. Following the implant, the Visual Analog Scale score was reduced to a mean of 1.6 from an initial mean score of 8.9. Three patients were completely weaned off opioid medications, while two patients continued to take opioid at a lower dosage. All patients experienced a decrease of the adjuvant neuropathic drugs.

Conclusion: Supraorbital/supratrochlear nerve stimulation appears to be a promising modality for the treatment of patients with intractable TAC.

Keywords: Cluster headaches, peripheral nerve stimulation, supraorbital nerve, supratrochlear nerve, trigeminal autonomic cephalalgia

INTRODUCTION

Headaches with prominent autonomic vasomotor symptoms are referred to as the trigeminal autonomic cephalalgias (TACs) and include episodic and chronic cluster headache (CH), short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headache with cranial autonomic features syndrome (1).

When chronically and medically intractable, these conditions have previously been treatable only with cranially invasive or neurally destructive methods.

Over the last decade, other types of drug-resistant intractable chronic headache, such as chronic migraine, occipital neuralgia, hemicrania continua, and chronic CH, have been shown to respond to treatment with suboccipital neurostimulation (2–5). Subcutaneous occipital nerve stimulation with unilateral or bilateral electrode arrays at the level of C1 has been developed into a relatively noninvasive technique for treating many of these intractable headache syndromes, with long-term results of 75–80% responder rate (6–10).

Intractable chronic CH is also being treated successfully with deep brain stimulation (DBS) (11–14). This approach, although efficacious, requires much more surgical precision and can produce much more severe consequences, including intracerebral hemorrhage and death (14).

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For those patients with intractable TAC who do not respond to suboccipital peripheral nerve stimulation, or who might not be candidates for DBS, another option is stimulation of the trigeminal nerve branches. A few cases of supraorbital nerve stimulation for other types of facial pain have been reported. In one retrospective case series, ten subjects had permanent implantation of a supraorbital nerve stimulator for the treatment of chronic, intractable frontal and frontotemporal headaches which were unresponsive to medication (15). Permanent implantation resulted in significant reductions in pain and use of opiate pain medications. Adverse events were minor, limited to three patients who had lead migrations and one with a minor scalp infection. Reed et al. recently reported on seven patients who were successfully treated for intractable chronic migraine with dual stimulation of both the occipital and supraorbital nerves (16). Slavin et al. reported on five patients undergoing supraorbital nerve stimulation for craniofacial pain (17). Another single case report of supraorbital nerve stimulation for supraorbital neuralgia was also published (18).

To our knowledge, only one prior report using strictly supraorbital stimulation for the treatment of chronic CH has been published (19).

We have been unable to discover any prior published reports about treatment of SUNCT with supraorbital stimulation, although Goadsby reported 50% success in treating two patients with occipital nerve stimulation (20).

In a review of neurostimulation for primary headache disorders in 2009, Schwedt recommended that "Further studies are required to determine the safety and efficacy of supraorbital nerve stimulation for treating headache disorders" (21).

MATERIALS AND METHODS

The present evaluation was conducted in the United States and involved four patients with intractable CH and one patient with intractable SUNCT syndrome. There were two study sites, and the patients were referred from a large neurology practice specializing in the treatment of headaches. The diagnosis was made in accordance with the International Headache Society classification (1).

The Asentral Institutional Review Board approved the study protocol #: 2009-147 A. The mean age $\pm$ SD was 52 $\pm$ 13.4. The mean duration of the symptoms $\pm$ SD was 14.4 years $\pm$ 12.6. There were three male and two female patients (Table 1). Four patients were diagnosed with CH and only one patient was diagnosed with SUNCT syndrome.

Table 1. Patient Demographics.	
Age (years)	
Mean (±SD)	52 (±13.4)
Range	35–68
Duration of symptoms (years)	
Mean (±SD)	14.4 (±12.6)
Range	1–30
Gender	
Male: N (%)	3 (60%)
Female: N (%)	2 (40%)
VAS scores (mean ± SD)	
Baseline	8.9 (±1.7)
Follow-up	1.6 (±1.1)
SD, standard deviation; VAS, Visual Analog Scale.	

The inclusion criteria were: 1) failure of extensive conservative treatments, including nonsteroidal anti-inflammatory drugs, abortive and prophylactic therapy drugs, neuropathic medications, and opioid drugs; 2) failure of long-term response to nerve blocks, including occipital nerve blocks, supraorbital blocks, and sphenopalatine ganglion radiofrequency ablation; 3) psychological evaluation clearance ruled out major depressive symptoms, illicit drugs or alcohol abuse, and secondary gains.

Procedure

A trial of peripheral stimulation was initially conducted for all patients. Three patients had a single supraorbital Octrode (St. Jude Medical Neuromodulation Division, Plano, TX, USA) trial lead, one patient had bilateral supraorbital trial lead placement, and a fifth patient had a supraorbital, infraorbital, and maxillary lead (Table 2). The choice of the trial stimulation was left to the discretion of the treating surgeon, based primarily on the location of the symptoms. Of note is that the patient with SUNCT syndrome had just one trial lead. One patient failed a trial of occipital stimulation but had a positive response to a subsequent trial of supraorbital nerve stimulation.

The placement of the trial lead was done in the operating room under light intravenous sedation. The area was prepped and draped in the usual sterile fashion. The patient was placed in a supine position and Octrode leads were placed via a 14-gauge Coudé needle (Epimed, Johnstown, NY, USA). For the supraorbital placement the needle was inserted approximately 2 cm above the supraorbital margin of the frontal bone. Local anesthesia was provided with lidocaine 1%, making sure that the area of the supraorbital nerve was not anesthetized. The tip of the needle was advanced under fluoroscopic guidance to approximately 0.5 cm lateral to the glabella line. Care was taken so that the needle remained in the subcutaneous layer and away from the skin. We prefer to use a Coudé needle, which is bent in a steeper angle and therefore becomes more steerable than the regular Tuohy needle, especially when the patients have a thin layer of subcutaneous tissue. Intraoperative testing was performed to ensure that stimulation was perceived over the area of nerve distribution. The lead was anchored or taped to the skin and the trial was conducted over six to eight days.

The patients were appropriately instructed on how to use the handheld Multiprogram Trial Stimulator (St. Jude Medical Neuromodulation) and they received a few programs to try at home. The criteria for implantation were meaningful pain relief, with a decrease of the Visual Analog Scale score of 50% or higher. All the patients found significant pain relief for the duration of the trial and no adverse side-effects. It was therefore decided to proceed with surgical implantation.

The actual implant was performed under general anesthesia. The patient was placed in a lateral decubitus position. The area was shaved, prepped, and draped in the usual sterile fashion. For the supraorbital implantation, a small 1.5-cm horizontal incision was made above the zygomatic process of the frontal bone, and just behind the hairline. Under fluoroscopic guidance, the Coudé needle was advanced in the subcutaneous tissue, parallel and 2 cm above the supraorbital margin of the frontal bone. This ensures that the contacts covered both the supraorbital and supratrochlear nerves as they ascend and divide into small branches along the medial and central area of the supraorbital space. The final lead position was documented by fluoroscopy (Fig. 1). Similarly, the patient with the three-lead implant had the additional infraorbital and maxillary leads placed in the same manner in the subcutaneous tissue. After

Table 2. Case by Case Data.

Case	# of leads	Lead placement	Initial VAS 0–10 scale	Follow-up VAS 0–10 scale	Duration of follow-up (months)	Work status	Device at follow-up	Complications	Diagnosis	Paresthesia coverage
1	2	Supraorbital	10	0	18	Retired	Functional	None	Cluster HA	
2	2	Bilateral supraorbital	9	3	24	Disabled	Explanted—needed MRI	None	Cluster HA	
3	3	Supraorbital infraorbital maxillary	9.2	2	36	Retired	Explanted—needed AICD implanted	Skin erosion	Cluster HA	
4	1	Supraorbital	10	1	24	Continues to work	Functional	None	Cluster HA	
5	1	Supraorbital	6	2	36	Disabled	Functional	Skin erosion, superficial infection	SUNCT syndrome	

AICD, automatic implantable cardioverter defibrillator; HA, headache; SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; VAS, Visual Analog Scale.
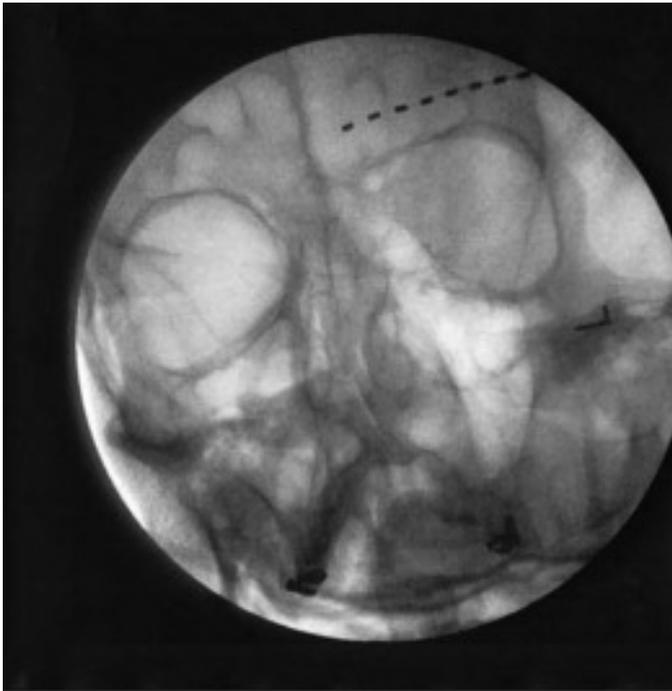
Figure 1. Single electrode (supraorbital) lead in final position.

this, the lead was anchored to the underlying superficial fascia with a silicon cigar-shaped anchor and silk sutures. For the tunneling of the lead wire the authors prefer a retro-auricular approach, which offers an aesthetic advantage, avoiding trauma to the facial tissue and nerves. A 0.5-cm cut-down incision was made in the suboccipital area and the lead wire was brought via the tunneling tool to the infraclavicular subcutaneous pocket above the pectoralis muscle.

The lead was subsequently connected to the internal pulse generator (Eon IPG, St. Jude Medical Neuromodulation Division).

RESULTS

The mean duration of the follow-up $\pm$ SD was 25.2 months $\pm$ 10.7. Two patients were explanted because of the need to place an automatic implantable cardioverter defibrillator or the need to perform magnetic resonance imaging tests. These two patients had been followed up for three and two years, respectively. The first patient had the pain well controlled with the device. When the device was removed, the pain returned immediately and he had to be placed on increasing doses of opioids to tolerate the pain. Within a year the patient died of a cardiac event.

The second patient had resolution of the pain 18 months after the implant. After that the patient did not require any stimulation, and when the device was removed the pain did not recur.

All patients reported improvement in their functional status with regard to activities of daily living and social interactions. Given that this was a retrospective study, we did not analyze objectively the overall functional improvement. At the end of the follow-up period, the Visual Analog Scale score was reduced to a mean of 1.6 from an initial mean of 8.9. Improvement was observed in both the frequency and the intensity of the painful attacks.

The main complications were skin erosion, which occurred in the patient with the three-lead implant and another skin erosion with secondary superficial infection at the site of the forehead skin covering the lead in another patient.

The superficial infection occurred one year after the implant and required a lead revision, which was successfully performed. The patient regained excellent coverage with good pain relief following reimplantation. In the other patient, the skin erosion occurred three years after the implantation. At that time the facial pain had

Figure 2. Scarring resulting from the lead placement. The small arrow shows the scar for the lead placement behind the hairline. The long arrow shows the scar for the pulse generator, three weeks after the implant.

resolved and because he needed an automatic implantable cardioverter defibrillator implant, the device was explanted without any further complications.

No additional significant adverse effects of implantation or neurostimulation were observed in any of the patients. All the patients were pleased about the aesthetic appearance of the facial surgical scars (Fig. 2).

There was no change in the work status: two patients remained disabled, two patients had been retired at the time of the implantation, and one patient continued to work full time after the surgery.

Three patients were completely weaned off opioid medications, while two patients continued to take opioid at a lower dosage. All patients experienced a decrease of the adjuvant neuropathic drugs (Table 3). The stimulation parameters revealed a low frequency ranging between 30 and 80 Hz. The pulse width ranged between 200 and 351 μsec and in all patients the amplitude was below 3 mA.

DISCUSSION

CH and SUNCT are non-migraine headache syndromes, which characteristically display autonomic features. These are two excruciating pain conditions with potentially devastating long-term effects. CH is a less prevalent type of headache compared with chronic migraine, and although its exact prevalence is unknown, it is estimated that CH occurs in 1–3 per thousand of the general population, with a gender (M : F) ratio of about 3:1 (22).

As with migraine, CH and SUNCT syndrome are primary headache types, meaning that they cannot be attributed to the presence of any other structural or organic cause, such as a brain tumor. It is possible that the risk for CH is higher in families with a positive history of CHs (23).

The clinical features of CH are quite distinct, especially when compared with migraine. The patients experience attacks of excruciating, strictly unilateral pain orbitally, supraorbitally, and/or temporally which occur from every other day, up to eight times per day, and last for 15–180 min. Each attack is associated with one or more of the following features of trigeminal autonomic activation: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, or miosis, ptosis, and periorbital edema (partial Horner's syndrome). The individual attacks occur in series lasting for weeks or months (so-called cluster periods), which are separated by remission periods usually lasting months or years (episodic CH). The attacks of the chronic CH are less frequent and occur for more than 12 months without remission periods or with remission periods lasting less than one month. The four patients in the present study presented with the chronic variant of CH.

SUNCT is less frequent than CH and displays the same autonomic features, albeit the attacks are of shorter duration (5–240 sec); hence, this condition can mimic tic douloureux. Another distinctive feature is the frequency of the painful attacks: the attacks are more frequent and the patient can experience from dozens to hundreds of attacks a day (24). Like CH, SUNCT appears to be more prevalent in males than females, although the ratio is lower: 1.5:1 (25).

Several pharmacologic agents are available to treat chronic CH, but few double-blind, randomized clinical trials have been conducted on these agents in recent years, and the quality of the evidence supporting their use is often low, particularly for preventive agents.

Verapamil and lithium are the first-line preventive agents for chronic CH (26). Unfortunately, approximately 20% of the patients fail to respond to pharmacological therapy, and more invasive interventional therapies are required (27). There are two ablative procedures described in the literature: sphenopalatine ganglion (SPG) radiofrequency ablation and gamma knife stereotactic radiosurgery (28–30). Three neuromodulation interventions are occipital nerve stimulation, vagus nerve stimulation, and hypothalamic stimulation (9,31–38).

Most recently, high epidural spinal cord stimulation has been used with good success in seven patients suffering from intractable CH (39). On a technical note, the epidural lead was placed in the upper cervical spine until further lead movement was stopped by the occipital bone or the posterior arch of the atlas.

The literature also reports one case of intractable episodic CH treated successfully with percutaneous cervical zygapophyseal radiofrequency ablation (40). The rationale was explained on the basis of an interaction or convergence within the cervical spine between pain pathways for the neck and head. Radiofrequency ablation of the SPG appears to be more effective for episodic CH (30) but can result in complications such as hypesthesia of the palate and epistaxis. In fact, the effectiveness of radiofrequency ablation and occipital nerve stimulation was only evaluated in observational studies, resulting in a 2C+ recommendation (5). Likewise the SPG can be amenable to electrical stimulation using the classical infrazygomatic approach during an acute episode of CH and the relief of pain occurs after several minutes of stimulation (41,42).

Gamma knife stereotactic single-session focused irradiation of the trigeminal nerve root is sometimes coupled with irradiation of the SPG as well. Stereotactic radiosurgery provides early pain relief in most patients, but is associated with trigeminal sensory dysfunction in some patients. Preliminary results, however, indicate that hypothalamic stimulation is associated with marked reduction of

Table 3. Medications Before and After Treatment.

Patient	Diagnosis	Medication preoperative	Medication postoperative
1	Cluster HA	Hydrocodone—8 pills/day 7.5 mg	None
		Klonopin—2 mg q.i.d.	Klonopin—1 mg t.i.d.
		Gabapentin—4 gm/day	Gabapentin n—2.4 gm/day
		None	Oxycodone—5 mg t.i.d.
2	Cluster HA	Methadone—20 mg/day	None
		Duloxetine—90 mg/day	Duloxetine—90 mg/day
		Lamotrigine—25 mg/day	None
3	Cluster HA	Cyclobenzaprine—10 mg/day prn	None
		Naprosyn—500 mg/day	None
		Diclofenac patch 1.3%	None
		Sumatriptan—100 mg prn	Sumatriptan—100 mg prn
		Darvocet—N-100 PRN	None
		Hydrocodone—5/500 prn	None
4	Cluster HA	Gabapentin—600 mg t.i.d.	Gabapentin—300 mg t.i.d.
		Verapamil—480 mg/day	None
		Indocin—25 mg q.i.d.	None
		Amitriptyline—10 mg q.d.	Amitriptyline—10 mg q.d.
		Tramadol—50 mg t.i.d.	None
5	SUNCT syndrome	Verapamil—240 mg b.i.d.	Verapamil—240 mg q.d.
		Topiramate—25 mg b.i.d.	None
		Baclofen—10 mg t.i.d.	None
		Oxycodone—90 mg/day	None
		Morphine—240 mg/day	None
		None	Morphine sulfate—80 mg b.i.d.

Medications before and after treatment.
HA, headache; SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

direct costs in the management of complete drug-resistant chronic CH (27).

The largest study of occipital stimulation was published by Burns et al. (38) and included 14 patients with medically intractable chronic CH. The median duration of follow-up was 20 months, which is comparable to our study. A total of six patients reported meaningful improvement of the pain. Improvement evolved over weeks or months, although attacks returned in a few days when the device malfunctioned due to battery depletion. The adverse events were related to one case of lead migration and four cases of battery depletion. The general impression from the few studies using occipital stimulation for patients with intractable CH is that relief occurred slowly over time and autonomic phenomena appeared to persist (33).

One study of supraorbital stimulation was performed in ten patients with localized intractable supraorbital neuralgia. After a period of 30 weeks of follow-up, the headache scores decreased and opioid consumption was reduced in half (15). Other studies found supraorbital nerve stimulation effective in relieving neuropathic facial pain including ophthalmic postherpetic neuralgia (43–45).

The mechanism of pain relief for patients undergoing peripheral nerve stimulation remains elusive, despite some prevailing theories, including increased local blood flow, increased serotonin and dopamine at the spinal cord level, inhibition of nociceptive responses of wide-dynamic-range neurons, and a possible alteration of pain inhibitory circuits (46–48).

Positron emission tomography scan studies using cerebral blood flow as a marker for neural activity performed before and during occipital nerve stimulation were very helpful in establishing the role of various brain structures such as the dorsal rostral pons in the pathophysiology of chronic migraine (49).

Because CH arises unilaterally in the first and second trigeminal nerve distribution (50), it makes sense to stimulate peripheral nerves, which in fact are branches of the trigeminal nerve. We found one case report of strictly supraorbital stimulation for one patient with chronic CH (19).

Another study looked at the treatment of seven patients with chronic intractable headaches using a combination of occipital nerve stimulation and supraorbital nerve stimulation. These patients were followed for a period ranging from 1 to 35 months. The authors concluded that this combination led to a substantially better outcome than occipital nerve stimulation alone (16).

Both the supratrochlear and supraorbital nerves are branches of the frontal nerve, which in turn is the largest branch of the ophthalmic division of the trigeminal nerve. Both nerves are amenable to stimulation as they emerge from the orbit and further divide into their terminal branches, which supply the skin of the forehead. Following the intuitive and practical wisdom of directly stimulating the peripheral nerves at the area of maximum nociception when they traverse underneath the subcutaneous tissue, it seems logical to attempt stimulating both nerves in the supraorbital area. The supratrochlear nerve ascends medially under the corrugator and frontal belly of the occipitofrontalis muscles to supply the skin of the lower part of the forehead. The supraorbital nerve passes via the supraorbital foramen and then ascends lateral to the supratrochlear nerve to finally divide into a smaller medial and a larger lateral branch. Both these branches are situated in the frontal belly of the occipitofrontalis muscle and then pierce the muscle and the epicranial aponeurosis.

Clearly, direct stimulation of a peripheral nerve is less invasive and a safer procedure compared with DBS (51). Also, because central sensitization mechanisms appear to play a significant role in the

pathophysiology of CH (52), it makes more sense to seek a neuro-modulation technique for the treatment of this condition. Moreover, intracranialor neurodestructive techniques are more invasive and pose additional risks of cerebral hematoma, permanent brain damage, and death (14).

In conclusion, based on this observational, open-label, and retrospective study, supraorbital/supratrochlear peripheral nerve stimulation appears to be a fairly safe and potentially effective therapeutic modality for patients with intractable TAC. Further efforts should be made to design a thinner and more compact lead to avoid the risks of skin erosion. Because of this cosmetically devastating complication, the implanter should discuss this potential risk with the patient, avoid treating patients who are on a chronic steroid therapy, and try to implant just one lead. Similar to occipital nerve stimulation, it appears that supraorbital nerve blocks do not accurately predict who will respond to a trial of supraorbital/supratrochlear nerve stimulation (17).

Replication and prospective larger controlled studies are needed for validation of this new modality. This may ultimately facilitate coverage of these procedures from third-party payers.

Authorship Statements

Dr. Vaisman prepared the manuscript draft and data collection. Dr. Markley, Dr. Ordia, and Dr. Deer provided important intellectual input for the preparation of the manuscript. All authors have approved the submitted version of the manuscript.

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