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Gamma Knife® Radiosurgery of the Trigeminal Nerve and Sphenopalatine Ganglion for Cluster Headache

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Abstract

Introduction: Cluster headache is a particularly severe, periodic cephalalgia which is occasionally refractory to medical treatment. In the past, surgical lesions of the trigeminal nerve (TN) have produced initial relief in more than one-half of patients. Radiosurgical lesions of the TN have produced short-lived pain relief and perhaps increased toxicity. In this pilot study we added the sphenopalatine ganglion (SPG) as an additional target in an effort to extend the degree and length of pain relief. **Methods:** Over an 8-year period, we carried out 12 gamma knife radiosurgical treatments in 7 patients, treating only the TN or later both the TN and SPG contemporaneously. A 4-mm collimated shot was placed on the nerve root entry zone of the TN and a maximum dose of 85 to 103 Gy was prescribed. The SPG was radiated in the pterygopalatine fossa using an 8-mm collimated shot and maximum dose of 85 to 97 Gy. **Results:** One patient with three treatments to the TN enjoyed immediate and complete relief for 5, 22, and 25 months. Four of 5 patients with radiation of both the TN and SPG experienced pain relief for 8 and 30 months, or are continuing to enjoy pain relief 7, 18, and 22 months after treatment or re-treatment at the last follow-up. Most patients reported facial paresthesias following radiation. No profound numbness or deafferentation pain was experienced. **Conclusions:** These results, in some respects, reflect the morbidity and pain relief experience of Gamma Knife® radiosurgery for classical trigeminal neuralgia. The addition of the SPG as a target may prove to be valuable and has not increased the morbidity of treatment.

Cluster headache (CH) is perhaps the most painful of all the cephalalgias and suicide is not a rare complication of unsuccessful treatment [1]. It is characterized by the International Headache Society as unilateral, periorbital, supraorbital or temporal pain lasting between 15 and 180 min. Cluster attacks are associated with parasympathetic discharge in the same region: lacrimation, conjunctival injection, rhinorrhea, nasal congestion, Horner's syndrome, eyelid edema, and ipsilateral facial sweating. A majority of sufferers experience restlessness and agitation during the attacks which can progress to violent behavior. CH is further characterized by its circadian and circannual periodicity [2]. Most individuals experience short bursts of pain, lasting minutes to hours, occurring several times a day for days to weeks. These cluster periods are followed by pain-free intervals lasting months to years. Attacks often reoccur at night or during the spring. A majority experience this episodic form of CH. Chronic CH sufferers have clusters lasting more than 1 year without remission and number about one-fifth of CH patients. CHs may be precipitated by alcohol, chocolate, histamine or nitroglycerine during the cluster period [1, 3, 4]. Other trigeminal autonomic cephalalgias are very rare [5]. They differ from CH by exhibiting more frequent daily attacks of shorter duration; having a female predilection and being prevented by indomethacin (paroxysmal hemicrania), or very frequent, extremely short duration with tearing and lacrimation (SUNCT) [4].

Medical treatment of CH is usually effective, especially in episodic cases. Acute treatment includes the use of subcutaneous sumatriptan and inhaled 100% oxygen. Effective prophylactic medications include verapamil and steroids, among other drugs [3, 6–8]. The overuse of medication among these patients may be significant [9]. Some patients become refractory to medical treatment and suffer greatly. It is estimated that 20% of chronic cases of CH are not controlled by medications [10]. Many surgical procedures have been reported for those patients who failed medical management.

There are few reports of radiosurgery for CH. Four studies outline the results of radiosurgery of the trigeminal nerve (TN) [11–14]. Three additional studies describe single patient experiences in treating the sphenopalatine ganglion (SPG) with radiosurgery [15–17]. We report our experience in treating both the SPG and the TN with Gamma Knife® radiosurgery for CH.

Materials and Methods

Between 1999 and 2008, we carried out 12 radiosurgical procedures on 7 patients with chronic or episodic CH at the San Diego Gamma Knife® Center. One patient was treated on five occasions over an 8-year period. Treatments were carried out using the Leksell Gamma Knife® Model U or the Leksell Gamma Knife® 4 C (Elekta AB, Stockholm, Sweden). On the day of treatment a Leksell Model G stereotactic head frame was placed and the patients underwent imaging. We use the Siemens Symphony 1.5 Tesla scanner (Siemens AG, Munich, Germany). Volumetric images are acquired in the sagittal plane using a MPRAGE protocol (TR 11.08, TE 4.3, flip angle 12°, slab thickness 220 mm), 1 mm thick, and contiguous

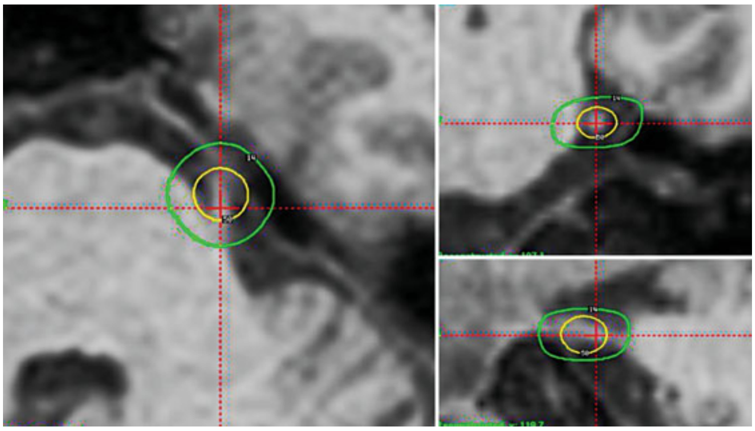

Fig. 1. Typical treatment plan for the TN showing the 50% isodose curve of a 4-mm collimator centered on the nerve entry zone, and the isodose curve corresponding to the 12-Gy dose overlapping the pons.

slices. The images were reconstructed into the axial plane before transferring the image data to the treatment planning computer. Additionally, we obtained a volumetric CT scan of the head with GE units. Images were 1.0 or 1.25 mm thick and contiguous. Contrast enhancement was not routinely used for MR or CT imaging.

Using the GammaPlan software, a 4-mm collimated isocenter was placed on the TN entry zone and a maximum dose of 85–103 Gy was prescribed for treatment. A portion of the 12-Gy isodose curve overlapped the pons and the center of the 50% isodose curve was 3–4 mm anterior to the junction of the nerve and the pons (fig. 1). This is the standard treatment protocol for treating trigeminal neuralgia in our center and common to other centers [18–21]. Clinical characteristics and treatment data are presented in table 1.

The SPG was identified in the pterygopalatine fossa using the CT and MR images [16, 22, 23]. An 8-mm collimated shot with a maximum dose of 85–97 Gy was used to treat the ganglion. The shot was positioned at, or just superior to the entrance of the vidian canal into the sphenopalatine fossa (fig. 2). We used lens blocking to reduce radiation dose to the lens. All patients were discharged on the day of treatment.

We contacted each patient by phone for information regarding the timing and degree of pain relief, as well as possible complications and the impact of treatment on their daily activities. Of the 7 patients, 5 were available for follow-up.

Results

The results of our 7-year experience in treating CH are presented in table 2. The average period of follow-up was 41 months and ranged from 11 to 100

Table 1. Clinical characteristics and treatment data for 5 patients treated with Gamma Knife® radiosurgery for cluster headache

Pat. No.	Age years	Duration of CH, years	Rx date	E/C	Dose TN	Dose SPG
1	37	15	07/13/1999	C	103	0
			05/26/2000		103	0
			06/12/2002		65	97
			03/02/2005		87	0
			06/06/2007		85	90
2	66	4	07/05/2006	C	90	0
3	58	41	03/01/2006	C	90	90
4	53	36	12/06/2006	E	85	85
5	49	11	02/07/2007	C	90	90
			12/27/2007		90	90

E = Episodic CH; C = chronic CH; TN = trigeminal nerve; SPG = sphenopalatine ganglion.Doses normalized to a 4-mm collimator output factor of 0.87.

months. All patients were male and the average duration of symptoms was 19 years, ranging from 4 to 36 years. Four patients suffered from chronic CH and 1 from episodic CH. Each patient was treated with contemporaneous radiosurgical lesions to the TN and SPG or single lesion to the TN only. Four of the 5 patients reported immediate pain relief and the pain relief was described as being 'pain-free' or 'nearly pain-free' by each individual.

Over a period of 8 years, patient 1 underwent five radiosurgical procedures with significant periods of pain relief. On three occasions the TN only was treated resulting in pain relief for 5, 25 and 22 months. Both the TN and SPG were radiated twice, producing pain relief for 30 months and continuing relief at his last follow-up after 7 months. Following the first radiosurgery to the TN he developed facial tingling as the pain remitted. After 5 months the tingling resolved as his cluster pain returned. Following his fifth treatment he again experienced facial tingling and reports some facial numbness.

Patients 2 and 3 with contemporaneous lesions of TN/SPG report continuing total or near-total pain relief at the last follow-up 18 and 22 months following radiosurgery. Patient 2 experienced facial tingling and formication 2 months after surgery, occurring several times a day. His Horner's syndrome disappeared and he was able to return to work as a business executive. He volunteered 'you

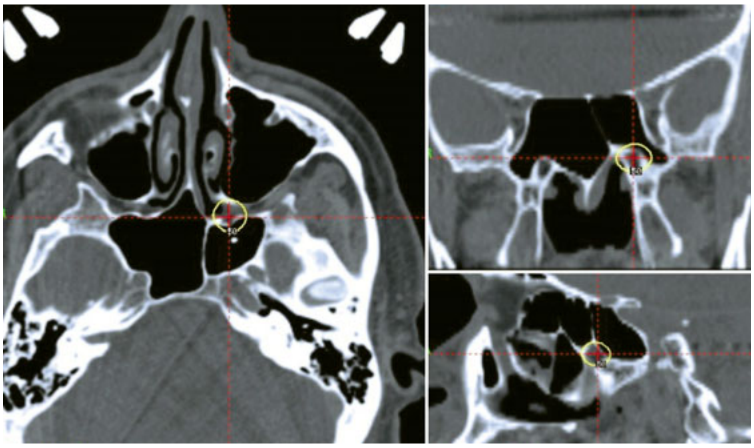

Fig. 2. Typical treatment plan for SPG. The 50% isodose curve of an 8-mm shot is located between the entrance of the foramen rotundum and the vidian canal into the pterygopalatine fossa.

have given me back my life.' Patient 3 suffered bothersome, but not painful paresthesias. He felt the treatment was 'lifesaving.'

Patient 4 was the only individual with episodic CH available for evaluation and he reported no pain relief after contemporaneous radiosurgery to the TN/SPG. He is the only individual reporting no facial paresthesias after treatment.

Patient 5 achieved significant pain relief for 8 months after contemporaneous radiosurgery of the TN/SPG. We recently retreated the TN and SPG. He experienced slight tingling in the face after his first radiosurgery.

Discussion

The recognition of the somatic, autonomic and periodic nature of CH pain has challenged the ingenuity of surgeons and led to a panoply of surgical interventions. Surgical remedies have been aimed at the hypothalamus, the central and peripheral trigeminal system and the autonomic nerves. Among these are interruption or decompression of the trigeminal tract, nerve, ganglion, roots, and nerves [24–31], interruption of the sympathetic pathways to the face [32], chemical or surgical interruption of the facial parasympathetic pathways to the face, including the nervus intermedius [27, 33], greater

Table 2. Clinical results of 5 patients treated with Gamma Knife® radiosurgery for cluster headache

Pat. No.	Rx date	E/C	Lesion site	Follow-up months	Onset pain relief, weeks	Duration pain, months
1	07/13/1999	C	TN		4	5
	05/26/2000		TN		2	25
	06/12/2002		TN, SPG		2	30
	03/02/2005		TN		2	22
	06/06/2007		TN, SPG	100	2	7[1]
2	07/05/2006	C	TN, SPG	18	3	18[1]
3	03/01/2006	C	TN, SPG	22	2	22[1]
4	12/06/2006	E	TN, SPG	13	N/R	N/R
5	02/07/2007	C	TN, SPG		2	8
	12/27/2007		TN, SPG	11		

E = Episodic CH; C = chronic CH; N/R = no result.
[1] Pain relief at last follow-up.

superficial petrosal nerve, and SPG [34–38]. Finally, stimulation, block and interruption of the vagus nerve [39], occipital nerve [40, 41] and most recently deep brain stimulation within the posterior hypothalamus have brought some pain relief [42, 43].

The most effective treatments seem to be lesions of the TN itself. Generally, the more sensory loss produced, the better the result. Sweet [31] reported immediate pain relief in 14 of 20 patients treated by radiofrequency lesion (RFL). A majority of patients reported pain relief after 5 years. Maxwell [25] found prolonged pain relief in all 8 patients treated, while Watson et al. [44] reported relief in 12 of 13 patients with RFL after 5 months' follow-up. Later, Onofrio and Campbell [24] reported excellent results in one-half of 26 patients treated by RFL or surgical section of the TN. Mathew and Hurt [45] found excellent relief in 15 of 27 with RFL, and Taha and Tew [46] reported immediate relief in 7 of 10 after RFL. Finally, 6 of 14 patients with complete TN section had good to excellent results after 5 years as reported by Kirkpatrick et al. [26]. An additional 4 patients with incomplete sections achieved relief with completion of the section. Interestingly, 2 patients continued to have pain despite complete nerve sections, indicating a central origin of the pain. It seems that more than one-half of patients can expect significant, immediate pain relief after TN lesions for CH, and the effect may last years.

However, long-term results in a large number of patients with episodic or chronic CH are lacking.

The results of Gamma Knife® radiosurgical lesions of the TN have been less promising than surgical lesions. RFLs produce more numbness than radiosurgical lesions. The initial report by Ford et al. [11] detailed 6 patients with CH treated with Gamma Knife® radiosurgery of the TN. Patients were followed only 8–14 months following 4-mm, 70-Gy shots to the TN entry zone. Ultimately, 4 patients were judged to have had excellent pain relief, 1 good and 1 fair pain relief. One patient reported transient tingling. Donnet et al. [12] twice reported a group of 10 patients with chronic CH treated with TN Gamma Knife® radiosurgery. The initial report with short follow-up (mean 13 months, range 8–21) detailed excellent results in 3 and good results in 3, although the results were contaminated by additional medical treatments. Lesions were placed at the cisternal portion of the TN and treated with a 4-mm isocenter to a maximum dose of 80–85 Gy. A subsequent report with longer follow-up [13] (mean 36 months, range 24–48) was less encouraging: 2/10 had complete relief of pain, 1/10 good and 7/10 no improvement. Virtually all patients developed paresthesias with or without hypoesthesia and 2 reported deafferentation pain. The complications were difficult to explain because the identical technique was used in Marseille to treat trigeminal neuralgia without the subsequent frequency and severity of facial sensory loss. They felt the TN may be unusually sensitive to radiation in patients suffering CH. Finally, McClelland et al. [14] treated 10 patients with 4- or 8-mm collimated shots close to the TN entry zone with a maximum dose of 83 Gy for chronic CH. Initially 60% reported good to excellent pain relief. At the final follow-up only 1 individual had fair pain relief and 9 had poor pain relief (40 months mean follow-up, range 5–88). One-half of patients reported facial numbness.

Radiosurgical lesions of the SPG for CH have been reported by Pollock and Kondziolka [15], DeSalles et al. [16], and Lad et al. [17]. Pollack treated a single patient with initial pain relief. The SPG was treated with a maximum dose of 90 Gy with an 8-mm shot. After 17 months the SPG was retreated with a maximum dose of 80 Gy with an 8-mm shot. After 2 years the patient remained pain-free. DeSalles treated 6 patients with complex facial pains exhibiting autonomic features. The SPG was radiated with a linear accelerator (BrainLAB – Novalis) using a 7.5-mm collimator and a maximum dose of 90 Gy. Only the single patient with CH achieved 'long-term pain relief.' Lad treated a single patient with chronic CH with a linear accelerator (Accuray-CyberKnife®). The sphenopalatine fossa was treated to a maximum dose of 65 Gy in a single fraction. After 12 months the patient reported a 50% reduction in pain frequency and severity.

There are no published reports of contemporaneous radiosurgical lesions of both the TN and the SPG. Seven patients with chronic CH were treated with radiosurgery to the TN/SPG by de Lotbinière et al. [47] and presented at the 12th International Meeting of the Leksell Gamma Knife® Society in Vienna in 2004. Patients were treated with 80- or 90-Gy, 4-mm shots to the TN and a 90-Gy, 8-mm shot to the SPG. After 3 years follow-up, 5 patients were reported to be pain-free and 1 had good relief. Two patients required retreatment during the follow-up period. Four of 7 patients developed facial numbness.

In this pilot study, patients were treated with Gamma Knife® radiosurgery to the TN and later to both the TN and SPG. Patient 1 achieved excellent pain relief for 5, 25 and 22 months after radiosurgery to the TN only. This result, in this single patient, is similar to the duration of pain relief reported by McClelland et al. [14]. Only after longer follow-up did their patients fail to experience pain relief. They did not recommend TN radiosurgery for CH because of 'a significant chance of morbidity…' and because 'even patients with excellent outcomes initially do not have sustainable results over time.' When viewed against the results of Gamma Knife® radiosurgery for classic trigeminal neuralgia however, the CH results may seem more acceptable. Following Gamma Knife® radiosurgery for classical trigeminal neuralgia, approximately 60% of patients are rendered pain-free after a hiatus of a few months. Rarely is pain relief immediate. 35% of patients report pain control while taking medications. A significant number report facial numbness. And about one-half of patients fail at 5 years [20, 21]. We do not consider facial paresthesias a complication of radiosurgery for tic, but a common sequela of successful radiosurgical treatment. We caution patients to expect facial tingling, and perhaps some numbness since intense radiation of the TN may damage the nerve.

Five responding patients underwent contemporaneous radiosurgery to the TN and SPG. Only patient 4 with episodic CH had no pain relief. Patient 1 reported excellent pain relief for 30 months following his first TN/SPG radiation, and continues to experience excellent pain relief 7 months after his second TN/SPG radiation. Patient 2 continues with excellent pain relief 18 months after treatment, and patient 3 continues with excellent pain relief 22 months after TN/SPG radiation. Patient 4 enjoyed excellent pain relief for 8 months and has recently been treated to the TN and SPG. All patients with pain relief reported the relief to be immediate. With longer follow-up the addition of the SPG target to radiosurgery of the TN may prove to be a benefit.

Four of 5 responding patients reported tingling in the face after radiosurgery to the TN/SPG. Only patient 4 experienced no facial tingling and he enjoyed no pain relief. Patient 3 experienced tingling which was at times 'bothersome' but not painful. The paresthesias peaked 6 months after treatment then subsided. These results do not confirm the 'high toxicity' of radiosurgery to the TN in patients with CH reported by Donnet et al. [13]. In our center a recent review of 263 patients treated for trigeminal neuralgia during the period 1994–2003 revealed a 63% rate of paresthesias reported occurring many months after radiation. Doses to the nerve entry zone ranged from 76 to 103 Gy (normalized to a 4-mm collimator output factor of 0.87). In most patients the tingling disappeared over time [unpubl. data]. No patients reported deafferentation pain. Similar results can be found in the literature, establishing the safety of contemporary doses to the TN in the treatment of trigeminal neuralgia [18–21]. There appear to be no complications of radiosurgical lesions of the SPG.

The symptoms of trigeminal neuralgia and CH are remarkably stereotypical. This fact begs a central, unifying theory of cause for both pain syndromes. In the case of trigeminal neuralgia, the cause is injury to the nerve entry zone at the pons by a vascular compression, tumor or demyelinating plaque in the majority of patients. In the case of CH, developments in neuroimaging suggest a central generator of the pain from the posterior hypothalamus [48]. The benefit of treatments to the peripheral TN (e.g. peripheral neurectomy, rhizotomy, etc.) in the treatment of trigeminal neuralgia suggests that centripetal sensory activity to the central pain generator plays a role in pain activation. Similarly, reduction in centripetal activity to the brainstem (e.g., occipital nerve block) in the treatment of CH also reduces pain activation. Treating the possible cause by deep brain stimulation within the posterior hypothalamus is appealing. Treating the peripheral sensory input is a valuable and time-proven advance in the treatment of trigeminal neuralgia and may become an advance in the treatment of CH.

We are encouraged to continue treating patients with chronic CH with contemporaneous radiosurgical lesions to the TN and SPG. There certainly remain several problems to be resolved: dose response, addition of other targets such as the vidian nerve in the vidian canal, long-term effectiveness, correct positioning of the lesion in the pterygopalatine fossa, among others. The disability and suffering of uncontrolled CH patients is enormous.

Conclusions

Contemporaneous treatment of the TN and SPG for CH produces rapid pain relief in more than one-half of patients with acceptable levels of facial tingling and numbness. Radiosurgery of the SPG alone has been shown to produce pain relief and the addition of this target to the TN may produce greater and more prolonged pain relief without additional morbidity.

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