PAPER

Gamma knife treatment for refractory cluster headache: prospective open trial

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Background: Since the initial report of Ford *et al* in 1998 no further study has evaluated radiosurgery of the trigeminal nerve in chronic cluster headache (CCH).
Methods: We carried out a prospective open trial of neurosurgery and enrolled 10 patients (nine men, one woman; mean age 49.8 years, range 32–77) presenting with severe and drug resistant CCH (mean duration 9 years, range 2–33). The cisternal segment of the nerve was targeted with a single 4 mm collimator (80–85 Gy max).
Results: The mean follow up was 13.2 months. No improvement was observed in two patients and three patients had no further attacks. Three patients showed dramatic improvement with a few attacks per month or very few attacks over the last six months. Two patients were pain free for only one and two weeks and their headaches recurred with the same severity as before. Three patients developed paraesthesia with no hypoaesthesia, one developed hypoaesthesia, and one developed deafferentation pain.
Conclusions: The rate and severity of trigeminal nerve injury appeared to be significantly higher than in trigeminal neuralgia, and this study does not support the positive results of the study of Ford *et al*. We consider the morbidity to be significant for the low rate of pain cessation, making this procedure less attractive even for the more severely affected subgroup of patients.

Cluster headache is one of the most debilitating headache syndromes. It is characterised by attacks of strictly unilateral, severe pain in an orbital, supraorbital, or temporal location. The attacks last 15–180 minutes and usually occur once or several times per day, especially at night, accompanied by ipsilateral conjunctival injection, lacrimation, rhinorrhoea, or nasal congestion and agitation.[1]

About 90% of people with cluster headache have the episodic form, but 10% have chronic cluster headache (CCH) in which the attacks are closely spaced with periods of remission lasting no longer than 30 days or pain without remission for more than a year. Once the chronic cluster syndrome is established, medical treatment is of limited success.[2] Hence, it is not surprising that various invasive and surgical procedures have been attempted in the hope of providing symptomatic relief. The clinical criteria for surgery in CCH are: total resistance to pharmacotherapy, headache ''locked'' to the same side; pain mainly in the region of the ophthalmic division of the trigeminal nerve; and psychologically stable individuals. The response to previous sphenopalatine ganglion blockade is not considered sufficiently specific to serve as an inclusion/exclusion criterion.[3]

Surgery has been carried out at many sites in an attempt to cure cluster headache[4]: interruption of the parasympathetic pathways by sectioning the intermedius nerve,[5] the greater superficial petrosal nerve, or the sphenopalatine ganglion,[6] or by lesioning of the trigeminal nerve.[7–9] In 1998, Ford *et al* reported positive results after radiosurgical targeting of the trigeminal nerve.[10] Since this initial report no other attempts have been made to evaluate trigeminal nerve radiosurgery in CCH and no long term follow up study has been published by Ford's team.

We organised a multicentre, prospective, self-controlled trial to evaluate strictly the safety and efficacy of gamma knife treatment (trigeminal nerve radiosurgery) in CCH. Here we report the preliminary results of the treatment.

PATIENTS AND METHOD

We carried out a multicentre (Marseille and Paris), prospective, non-blinded open trial of radiosurgery without clinical controls. Between January 2002 and February 2003, 10 patients (nine men, one woman) presenting with very severe and drug resistant CCH were enrolled. The candidates for gamma knife surgery were selected according to the following criteria: (*a*) the patient met the criteria of CCH as defined by the International Headache Society classification and (*b*) failure of appropriate drug treatment including verapamil (480–1200 mg per day) and lithium. Medical treatment was perceived to have failed on the basis that the physician administered optimal medications at high therapeutic serum concentrations. Previous prophylactic treatments are summarised in table 1. At the time of this data collection, the role of antiepileptic drugs in the treatment of CCH was not clearly defined. However, there are no established guidelines for medically intractable CCH.

The protocol of the prospective trial was submitted to the ethics committee and to the health authorities and modified according to their recommendations. An information brochure and explanation of the procedure was given to the patient and informed consent obtained. This was signed by the patient and the investigator. The experimental nature of the procedure was extensively explained. The specific risk of failure or side effects and especially the risk of hypoaesthesia and deafferentation pain was explained to the patients.

The patients were admitted to the Marseille Timone University Hospital the day before radiosurgery and discharged the day after (two nights). The frame was applied under local anaesthesia after administration of mild sedative medication. The frame was placed so that the base ring of the frame was parallel to the trigeminal nerve axis.[11]

Preoperative stereotactic imaging systematically included magnetic resonance (MR) and computed tomography (CT)

Abbreviation: CCH, chronic cluster headache

Table 1 Details of patients with chronic cluster headache enrolled in the present study

Patient	Age	Sex	Chronic since	No. of attacks/day	Failed previous prophylactic treatment	Date of gamma knife surgery
1	47	M	1985	1	Verapamil (840 mg/d); clomipramine (125 mg/d); amitriptyline (100 mg/d); gabapentin (3600 mg/d); valproate (1g/d); indometacin (150 mg/d); methysergide (4.95 mg/d); propranolol (80 mg/d); lithium (750 mg/d); baclofen (75 mg/d)	02/01/02
2	52	M	1992	5–6	Verapamil (720 mg/d); lithium (750 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d); propranolol (120 mg/d); two occipital nerve blockades: 1996 and 1999	05/02/02
3	60	M	2000	2	Verapamil (720 mg/d); lithium (750 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d); propranolol (160 mg/d); two occipital nerve blockades: 2001 and 2002	06/06/02
4	43	M	2000	1	Verapamil (600 mg/d); lithium (750 mg/d); amitriptyline (100 mg/d); clomipramine (75 mg/d); valproate (1 g/d; successful but pancreatitis); topiramate (100 mg/d; adverse effects ++); gabapentin (1.2 g/d)	27/06/02
5	35	M	2000	1	Verapamil (720 mg/d); lithium (750 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d)	05/07/02
6	62	M	2002	3	Verapamil (960 mg/d); lithium (750 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d)	17/10/02
7	50	M	1998	2	Verapamil (720 mg/d); lithium (750 mg/d); valproate (1.5g/d); indometacin (200 mg/d); propranolol (160 mg/d)	05/11/02
8	77	F	1970	1	Verapamil (960 mg/d); lithium (750 mg/d); topiramate (150 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d)	21/01/03
9	32	M	2000	6	Verapamil (720 mg/d); lithium (750 mg/d); valproate (1.5g/d); occipital nerve blockade: 2001	18/02/03
10	40	M	1995	5	Verapamil (720 mg/d); lithium (750 mg/d); methysergide (4.95 mg/d); indometacin (200 mg/d); two occipital nerve blockades: 1999 and 2000	25/02/03

scans. The MR (Siemens 1.5 Tesla) sequences included a T2 high resolution (0.5 mm) three dimensional acquisition (CISS; constructive interference study state sequence from Siemens) acquired in the axial plan and a three dimensional T1 acquisition (MPR) 1.5 mm thick. CT scan bone window acquisition served as part of the quality control to check and eventually correct the distortion of the MR images.[10] The cisternal segment of the nerve (defined as the part between Meckel's cave and the pons) was targeted with a single 4 mm collimator. The target used in this study was exactly the same as the one we are using for essential trigeminal neuralgia—the anterior aspect of the cisternal segment of the nerve partially overlapping the plexus triangularis.[12] The target was set as anteriorly as possible in the cistern to cover the plexus triangularis and to decrease the energy delivered to the brainstem. The maximum dose (100%) as defined in the protocol was 80–85 Gy. It was 80 Gy in nine patients and 85 Gy in one patient. A model C gamma knife (Elekta AB, Stockholm) was used for the radiosurgical procedure.

RESULTS

The mean age of the 10 patients was 49.8 years (range 32–77) and mean duration of the cluster headache was 9 years (range 2–33). The patients were followed up for a mean of 13.2 months (range 8–21) and evaluated at 3, 6, and 12 months. For evaluation of the treatment results, the patients were divided into four categories: excellent, good, fair, and failure. The result was considered to be excellent if the patient was free of cluster headache and took minimal or no medication, and good if the cluster headache reduced in severity and frequency by 50% and prophylactic medications were continued. Fair results indicated improvement of 25% or less, with continued use of prophylactic treatment. Patients with no relief at all were considered failures. The results at one year are detailed in table 2.

Three patients had complete relief from CCH (patients 3, 9, and 10), of whom one (patient 9) was on prophylactic treatment during follow up; patients 9 and 10 had the shortest follow up and the experience of other surgical methods demonstrated that an initial response can be obtained followed by recurrence. Patient 3 had no further medical treatment. This patient underwent greater occipital nerve blockade on day 37 with complete cessation of pain. He had been treated before with this technique but had never had such a long remission—in this case, it is difficult to state which technique led to complete relief.

Three patients showed dramatic improvement with a few attacks per month or very few attacks over the last six months (patients 2, 5, and 6). We considered their results good, and they continued to use preventive medications. Three patients had immediate relief of CCH or were free of attacks within a week following gamma knife surgery. There is no explanation for this and was also reported by Ford *et al*.[10]

Two patients were pain free for only one and two weeks and had recurrence of cluster headache with the same severity and frequency as before (patients 1 and 4). No improvement was observed in two patients (failures; patients 7 and 8).

No patient sustained an immediate complication after the gamma knife procedure. Three patients developed paraesthesia with no hypoaesthesia, one developed hypoaesthesia, and one developed deafferentation pain. The severity of the deafferentation pain in this last patient (patient 1) led us to perform a cortical stimulation.

DISCUSSION

Chronic cluster headache is the most severe primary headache syndrome known. Improvement has been reported with surgical procedures classically proposed for trigeminal neuralgia,[2] although with a low rate of pain cessation and a high rate of nerve damage. The pain and attacks of cluster headache might originate in or are mediated to a number of different sites: the regional orbital, internal or external carotid circulation, the cavernous sinus, the trigeminal vascular nervous connections, the sympathetic and parasympathetic nerves, and the hypothalamic centres (for review see references 13, 14).

The exact aetiology and pathophysiology of cluster headache is yet to be fully elucidated. However, this syndrome has three major features: trigeminal distribution of the pain, accompanying ipsilateral symptoms of autonomic dysfunction, and episodic pattern of the attacks. First, the cluster headache pain is localised to the distribution area of the ophthalmic division of the trigeminal nerve, with the maximum pain invariably centred in or around the eye or forehead. The pain threshold is reduced within this area during the cluster headache periods. It is logical to assume that facial pain must reach the central nervous system through the trigeminal sensory nerve fibres and that, just as in trigeminal neuralgia, interruption of some part of the trigeminal system may prevent the painful impulses reaching the pons. Secondly, the ipsilateral autonomic features reflect parasympathetic dysfunction. The parasympathetic fibres arise from

Table 2 Characteristics of the chronic cluster headache in ten patients following gamma knife surgery and follow up at one year

Patient	Evolution of the chronic cluster headache and follow up	Evaluation of treatment at one year/side effects
1	Completely disappeared for first 15 days Initially pain attacks less frequent 21 months follow up: pain as severe as before (1 attack/day) with prophylactic treatment (verapamil 600 mg/d; clomipramine 150 mg/d)	Failure/hypoaesthesia Deafferentation pain++
2	June 2002: complete pain cessation 20 months follow up: 1 attack/month with prophylactic treatment (propranolol 160 mg/d)	Good/0
3	Until day 7 no pain Day 7 to 11: 2 attacks/day Day 37: greater occipital nerve blockade 15 months follow up: complete pain cessation; no prophylactic treatment	Excellent/paraesthesia 15/08/02 no hypoaesthesia
4	Reduction in the frequency and severity of the pain attacks and complete stop at 1 week December 2002: return of pain as before 15 months follow up: prophylactic treatment (verapamil 480 mg/d)	Failure/0
5	Transient improvement at 5 months 13 months follow up: 4 attacks/month with prophylactic treatment (verapamil 480 mg/d)	Good/paraesthesia without hypoaesthesia
6	Complete disappearance of the pain at 5 months 12 months follow up: 2 attacks at 6 months; prophylactic treatment (verapamil 360 mg/d)	Good/hypoaesthesia No corneal reflex
7	No improvement at 11 months (verapamil 480 mg/d; lithium 250 mg/d)	Failure/paraesthesia (cheek)
8	No improvement at 9 months	Failure/0
9	No attacks in the last 6 months with treatment 8 months follow up: lithium 750 mg/d; valproate 2 g/d	Excellent/0
10	8 months follow up: no attack; no prophylactic treatment	Excellent/0

the superior salivatory nucleus, exit the brain stem via the nervus intermedius and may also run in the seventh or eighth cranial nerves.[2] Finally, the episodic and often time related consistency and seasonal predilection of attacks bears the signature of a dysfunctional central pacemaker which may be situated in the hypothalamus. In fact procedures targeting the trigeminal pathway have been employed, alcohol injection in the gasserian ganglion, root section of the trigeminal nerve,[8 15 16] glycerol rhizotomy,[3] radiofrequency (RF) rhizolysis of the trigeminal nerve,[7] and microvascular decompression of the trigeminal nerve or the nervus intermedius.[17]

Gamma knife radiosurgery is now a part of the available armamentarium for surgical therapy of essential trigeminal neuralgia. More recently this technique has been used in CCH,[10] targeting the trigeminal root entry zone in the pons. In this series, four men and two women with refractory CCH were treated with a dose of 70 Gy to the isocentre. Four of the six patients experienced excellent relief (defined as free from cluster headaches with minimal or no medication). One patient had good relief and the final patient's result was judged to be fair. No serious side effects were reported, however, the long term benefits were not evaluated in this study.

Among the proposed neurosurgical techniques, thermocoagulation of the trigeminal nerve or of the sphenopalatine ganglion and microvascular decompression have recently been re-evaluated. In 1997, Sanders and Zuurmond reported a series of 66 patients with refractory cluster headache treated with sphenopalatine ganglion blockade. Of these only 10 had CCH (and 56 episodic)[3] and complete pain relief was obtained in three of these patients (partial relief in three). In 1995, Taha and Tew reported a series of seven patients with refractory CCH treated with RF rhizotomy.[7] All the patients were reported to be pain free immediately after the procedure but at last follow up (median follow up five years; range 2–20 years) only two were still pain free (at seven and 20 years), and three had mild recurrence with good drug sensitivity. These authors reported one patient with complications (transient diplopia and keratitis). Two other series of patients who underwent trigeminal nerve root section confirmed that this procedure is an effective treatment with acceptable morbidity.[15 16] Finally, Lovely *et al*[2] reported a series of 20 patients with CCH who underwent microvascular decompression of the trigeminal nerve alone (n = 9), or with microvascular decompression of the nervus intermedius (n = 3), or with sectioning of the nervus intermedius (n = 10). At the last follow up more than 90% reduction in pain was achieved in 45% of patients (nine patients) and more than 50% reduction in pain in six patients. Complications included one infected cranioplasty requiring removal, one cerebrospinal fluid leakage requiring spinal drainage, seven patients with headache requiring a lumbar puncture, but no hearing loss or facial palsy was reported.

Our experience with radiosurgery does not compare very favourably with the results of these series. However, due to the frequency of recurrences, irrespective of the technique used, other options should not be neglected. In our study of gamma knife surgery for trigeminal neuralgia (276 procedures) in spite of the use of the same target and a similar dose, hypoaesthesia remained rare (n = 16; 5.8%), and we did not encounter severe hypoaesthesia associated with iatrogenic deafferentation pain (data under publication). Several hypotheses may be advanced to explain this intriguing discrepancy. Perhaps in patients with trigeminal neuralgia and structural alteration in the fifth cranial nerves this nerve is more resistant to radiosurgery. An alternative hypothesis may be an abnormal sensitivity of the nerve in CCH.

The rather high morbidity and low efficacy of radiosurgery directed towards the trigeminal nerve (at least in our hands) indicate that new therapeutic options should be explored. The first published results of posterior hypothalamic stimulation are encouraging.[18 19] A few authors have proposed directing radiosurgery towards the sphenopalatine ganglion or both the sphenopalatine ganglion[20] and the trigeminal nerve (Delotbinière, personal communication).

CONCLUSION

This first prospective evaluation of gamma knife surgery for cluster headache showed that complete pain cessation can be obtained over a significant period of time. However, long term evaluation is necessary. Our study does not support the positive results of the study of Ford *et al*.[10] The rate and severity of trigeminal nerve injury appear to be significantly higher than in trigeminal neuralgia.[21] We consider the

morbidity to be significant for a low rate of pain cessation making this procedure less attractive even for the more severely affected subgroup of patients. Our group is evaluating other approaches. Moreover, we propose that recommendations for the criteria of medically intractable cluster headache, such as those developed for medically intractable epilepsy, are necessary. The role of the new antiepileptic drugs, in particular topiramate,[22] in CCH has to be clarified.

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