Efficacy of Sphenopalatine Ganglion Radiofrequency in Refractory Chronic Cluster Headache

Laura Salgado-López[1], Cristian de Quintana-Schmidt[1], Robert Belvis Nieto[2], Carles Roig Arnall[2], Rodrigo Rodríguez Rodriguez[1], María Jesús Álvarez Holzapfel[1], Joan Molet-Teixidó[1]

■ BACKGROUND: **In the literature, there are only short series of radiofrequency of the sphenopalatine ganglion (SPG) to treat chronic refractory cluster headache (CCHr) with variable results. Furthermore, there is no consensus on which methodology to use: radiofrequency ablation (RFA) or pulsed radiofrequency (PRF).**

■ METHODS: **We conducted a prospective analysis of 37 patients with CCHr who underwent RFA or PRF of the SPG in our center between 2004 and 2015.**

■ RESULTS: **The mean age of the patients was 40 years (range, 26–59 years). PRF was performed in 24 patients, and RFA was performed in 13 patients. A total of 5 patients (13.5%) experienced complete clinical relief of both pain and parasympathetic symptoms, 21 patients (56.8%) had partial and transient relief, and 11 patients (29.7%) did not improve. There was no evidence of significant superiority of one radiofrequency modality over the other ($P = 0.48$). There were no complications associated with the technique. The passage of time tended to decrease the efficacy of both techniques ($P < 0.001$). The mean follow-up was 68.1 months (range, 15–148 months). To our knowledge, this is the series with the largest number of patients and the longest follow-up period published in the literature.**

■ CONCLUSIONS: **Radiofrequency of the SPG is a safe, fast, and partially effective method for the treatment of CCHr. Given its low rate of complications and its low economic cost, we think it should be one of the first invasive treatment options, prior to techniques with greater morbidity and mortality, such as neuromodulation.**

INTRODUCTION

Cluster headache (CH) is a severe and disabling primary headache that belongs to the group of autonomic trigeminal headaches. According to the criteria of the *International Classification of Headache Disorders 3rd Edition* (Table 1), it is characterized by episodic unilateral headache attacks ranging in duration from 15 to 180 minutes, accompanied by parasympathetic ipsilateral symptoms.[1] Approximately 10% of CHs are chronic, generating recurrent attacks with no pain free periods longer than 1 month for a minimum of 1 year, and 10% of them become refractory to pharmacologic treatments. Chronic refractory cluster headache (CCHr) is a devastating condition with profound negative effects on the life of patients, a fact that has led to it being known as the suicide headache.[2]

Being considered by some as the worst pain a human can experience,[3] several nonpharmacologic invasive methods have been used in these patients during the last decades.[4] These include injurious surgical procedures focusing primarily on the trigeminal ganglion and, more recently, techniques based on neuromodulation, both at central and peripheral levels.[5,6] These techniques include variable effectiveness rates and life-threatening complications.

Radiofrequency of the sphenopalatine ganglion (SPG) was described by Salar et al. in 1987.[7] Although the pathogenesis of CH has not been completely elucidated, the SPG has traditionally been

Key words
- Chronic cluster headache
- Pulsed radiofrequency
- Radiofrequency ablation
- Refractory
- Sphenopalatine ganglion

Abbreviations and Acronyms
CCHr: Chronic refractory cluster headache
CH: Cluster headache
PRF: Pulsed radiofrequency
RFA: Radiofrequency ablation
SPG: Sphenopalatine ganglion

From the Departments of [1]Neurosurgery and [2]Neurology, University Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

To whom correspondence should be addressed: Laura Salgado-López, M.D. [E-mail: lsalgado@santpau.cat]

Citation: World Neurosurg. (2019) 122:e262-e269.
https://doi.org/10.1016/j.wneu.2018.10.007

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

Table 1. Cluster Headache Criteria of the *International Classification of Headache Disorders, 3rd Edition*

A. At least 5 attacks fulfilling criteria B—D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15—180 minutes (when untreated)
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
a) Conjunctival injection and/or lacrimation
b) Nasal congestion and/or rhinorrhea
c) Eyelid edema
d) Forehead and facial sweating
e) Miosis and/or ptosis
2. A sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day
E. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3, International Classification of Headache Disorders, 3rd Edition.

considered to be involved in the pathophysiology of CH.[8,9] SPG radiofrequency is a quick and simple technique that has proven its efficacy in episodic CH, having been used in a short series of chronic CHs with variable results. Because the heat on the tip of the needle can be accurately controlled and regulated, it is theoretically considered the most selective method of blocking the SPG; however, there is no consensus on which methodology to use: radiofrequency ablation (RFA) or pulsed radiofrequency (PRF).[10,11]

This study prospectively evaluates the efficacy of SPG radiofrequency, based on data from 37 patients with CCHr, after a mean follow-up period of 68 months. We also analyze the complications of the technique and make a comparison between RFA and PRF. To our knowledge, this is the largest series of patients with the longest follow-up period published so far in the literature.

MATERIALS AND METHODS

Patients

After the approval of the study by the ethics committee of our hospital, the data were collected prospectively by means of pain diaries and questionnaires and reviewing medical notes.

Between 2004 and 2014, a total of 37 patients diagnosed with CCH according to the criteria of the *International Classification of Headache Disorders 3rd Edition* were treated.[1] All patients met the previously published criteria of treatment refractoriness. Because of the invasive nature of the technique, additional selection criteria were the duration of the chronic phase of at least 2 years and the absence of disabling organic or psychiatric diseases.

Among the previously performed procedures, we can highlight occipital nerve blocks, infiltrations with botulinum toxin, PRF of the cervical roots (C1 and C2), percutaneous Gasser ganglion compressions, trigeminal nerve vascular microdecompressions, SPG blockages, and testosterone injections.

The frequency and intensity of attacks, before and after each treatment, and the variation of the pharmacologic needs, the duration of the improvement phase, and the objectified complications were recorded.

A normal brain magnetic resonance imaging was an inclusion criterion. Only 2 patients presented relevant findings not related to chronic CH: a cerebral artery aneurysm contralateral to headache and a craniopharyngioma.

Prior informed consent to radiofrequency was obtained in all patients after an exhaustive explanation of the technique and possible therapeutic alternatives.

Technical Description

The patient is placed supine on the operating table, and the head is immobilized with an adhesive band. Under lateral fluoroscopic vision, the c-arm of the radiograph machine is rotated until both mandibular branches overlap and the pterygopalatine fossa, characteristically described as an inverted pyramid, is correctly visualized. The epidermal entry point is the mandibular notch. Then 1% lidocaine is injected into the skin to facilitate the introduction of the electrode. A needle of 22 gauge of caliber and 10 cm in length is used, with a straight active tip of 5 mm. The needle is first inserted under lateral fluoroscopic control and advanced medially and superiorly to the pterygopalatine fossa. As soon as the maxillary nerve is touched with the tip of the electrode, the patient will experience sharp pain. Once in the right direction, an anteroposterior view is obtained and the tip of the needle is advanced until it is positioned just laterally to the nasal wall, at the level of the middle turbinate. The needle guide is then replaced by the radiofrequency electrode (**Figure 1**).

To confirm the position is adequate, it is verified neurophysiologically by sensory stimulation at 50 Hz (in the case of PRF at 0.3—0.4 mA and in RFA at 0.2 mA). If the position is correct, the paresthesia will be perceived at the endonasal level. If paresthesia occurs on the cheek, upper teeth, or upper lip, that would indicate that stimulation is occurring in the maxillary nerve, and the needle should be repositioned caudal and medially. If the patient perceives paresthesia on the hard palate, it means that the major or minor palatine nerves are being stimulated, and then the electrode should be moved posterior, medial, and superiorly.

As soon as the location of the electrode is adequate, RFA or PRF is performed: with RFA, 0.5 cm^3 of 0.2% ropivacaine is injected first and a lesion is made at 80°C for 60 seconds, checking the sensitivity in the superior lip at all times. With PRF, a cycle is applied at 42°C and 40 V for 120 seconds.

All patients are placed a peripheral venous line before starting radiofrequency. The procedure is performed under electrocardiographic and vital signs monitoring.

Procedures

Because there is no scientific evidence to support the superiority of one radiofrequency modality over the other, the patients underwent RFA or PRF in accordance with the current protocol in our center at that time. Twenty-four patients underwent PRF, and 13 patients underwent RFA. Both modalities were repeated in those cases in which the response was partial or there was no improvement and the patients tolerated the first procedure, agreeing to perform a second attempt. Therefore, PRF was

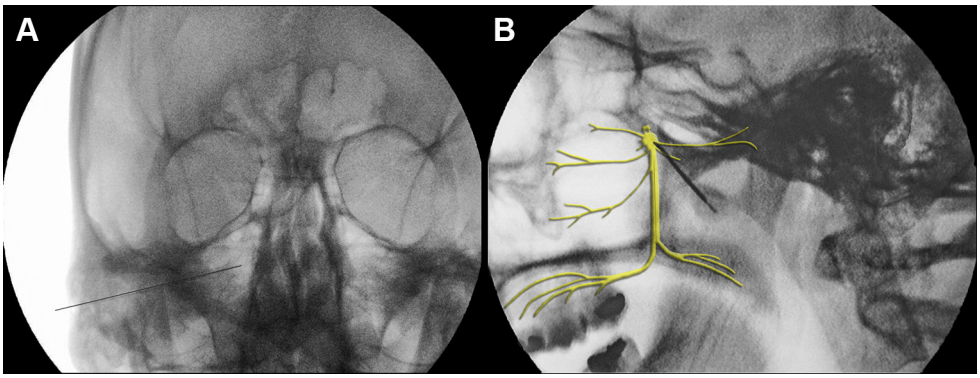

Figure 1. Intraoperative radiograph showing the correct placement of the radiofrequency needle inside the pterygopalatine fossa: (**A**) anterior-posterior radiograph and (**B**) lateral radiograph with the sphenopalatine ganglion and its main nerves.

repeated in 5 patients and RFA was repeated in 2 patients, performing a total of 44 procedures. The parameters used in each of the techniques and the initial location of the paresthesia experienced during their implementation were recorded.

Follow-Up

The evaluation of pain was performed by a visual analog scale. To perform the statistical analysis of pain intensity, the results were grouped as follows: mild (1) = scores 1–3, moderate (2) = scores 4–6, and severe (3) = scores 7–10. The result of radiofrequency was considered as complete symptomatic relief (complete response) if the patient stopped experiencing pain and parasympathetic symptoms, without the necessity of pharmacologic treatment. Partial result was defined as a decrease in the number of attacks or the intensity of the attacks resulting in a reduced pharmacologic need. No improvement was defined as no difference in pain pattern.

The first control visit was made 1 month after the procedure in all cases, spacing the successive visits at 3 months, 6 months, and thereafter annually.

Statistical Analysis

Variables were described using the number of cases and percentages for categorical variables and mean, median, and SD for quantitative variables. The results were analyzed using χ^2 for categorical variables and Mann-Whitney U test for ordinal and quantitative variables that did not follow a normal distribution. Wilcoxon signed-rank test, t test, and Cohen κ coefficient were also used. Statistically significant differences were considered when $P < 0.05$.

RESULTS

The main characteristics of each patient are summarized in Table 2.

In total, 37 patients were treated with radiofrequency: 29 patients were men (78%) and 8 were women (22%). The mean age at onset of headache was 31 years (range, 15–56 years), with the mean age of chronicity being 35 years (range, 21–56 years). The mean age at the time of the first treatment was 40 years (range, 26–59 years).

In 20 patients the affected side was the right, and in 17 patients the affected side was the left. Eleven patients presented chronic CH de novo, having evolved in the remaining 26 patients from the episodic form of CH.

The mean follow-up period was 68.1 months (range, 15–148 months). All patients completed the follow-up period, and there were no missing data.

The group of patients treated with PRF was similar to the RFA group in terms of baseline characteristics, number of drugs, and number and intensity of the attacks before the treatment.

Considering both types of radiofrequencies (RFA and PRF), a total of 5 patients (13.5%) experienced complete clinical headache relief of both pain and parasympathetic symptoms, 21 patients (56.7%) presented partial and transient relief, and 11 patients (29.7%) did not improve. In our series, there were no patients with improvement in pain and persistent autonomic symptoms, which has been previously described in the literature.[12,13] There were no complications associated with the technique in any of the cases. In all cases the procedure was performed ambulatory.

PRF was performed in 24 patients. There was an improvement in 17 patients (70.8%), with no improvement in 6 patients and worsening in 1 patient. Four patients presented a dramatic improvement with an absolute headache remission (16.7%), both of the headache and the parasympathetic component, which is maintained at this time. The mean duration of partial improvement was 4.7 months.

A total of 13 patients underwent RFA. Clinical improvement was observed in 8 patients (61.5%), with permanent disappearance of symptomatology in 1 patient, and no improvement in the remaining 5 patients. The mean duration of the partial improvement was 5.2 months.

The percentage of patients who presented clinical improvement with PRF was higher than with RFA (70.8% vs. 61.5%; respectively; $P = 0.48$). Additionally, the percentage of asymptomatic patients who were observed after PRF was also better than after RFA (16.7% vs. 7.7%, respectively; $P = 0.64$).

Table 2. Clinical Characteristics and Outcomes in the 37 Patients with Chronic Refractory Cluster Headache Treated by Radiofrequency

Patient Number	Sex	Onset Headache Age (Years)	Chronification Headache Age	First Treatment Age (Years)	Treatment Number	Daily Number of Attacks Pretreatment	Intensity of Attacks Pretreatment*	Daily Number of Attacks Posttreatment	Intensity of Attacks Posttreatment*	Number of Drugs Pretreatment	Number of Drugs Posttreatment	Improvement	Improvement Length (Months)	Asymptomatic
Pulsed radiofrequency														
1	Female	25	25	27	1	4	3	0	0	3	0	Yes	151	Yes
2	Female	41	41	42	1	4	3	4	3	4	2	No	0	No
					2	4	3	4	3	2	2	No	0	No
3	Male	19	22	34	1	3	2	2	2	7	1	Yes	1	No
4	Male	34	36	38	1	4	3	1	3	5	4	Yes	1	No
5	Male	35	43	46	1	2	2	0	1	4	0	Yes	94	Yes
6	Male	17	24	36	1	0.3	3	0	0	4	0	Yes	86	Yes
7	Male	22	34	42	1	1	3	1	3	6	4	No	0	No
					2	1	3	1	3	4	4	No	0	No
8	Female	36	44	46	1	4	3	1	2	7	0	Yes	18	No
9	Male	28	32	24	1	4	2	0	0	5	2	Yes	4	No
					2	5	2	1	2	2	2	Yes	1.5	No
10	Male	42	44	46	1	3	3	0	0	3	2	Yes	8	No
					2	2	3	0	0	6	2	Yes	4	No
11	Male	36	46	48	1	1	3	0	0	5	0	Yes	73	Yes
12	Male	37	38	40	1	4	3	4	3	5	5	No	0	No
13	Male	39	39	42	1	2	3	2	3	4	4	No	0	No
14	Male	37	41	42	1	0.8	2	0.07	2	2	1	Yes	7	No
15	Male	15	38	53	1	3	3	0.5	2	3	2	Yes	3	No
					2	2	3	0.7	2	2	2	Yes	2	No
16	Male	28	36	38	1	3	3	3	3	2	2	No	0	No
17	Male	21	24	27	1	4	3	1	3	4	4	Yes	1.5	No
18	Male	21	24	27	1	4	3	3	2	2	2	Yes	7	No
19	Male	22	24	30	1	4	3	1	3	2	2	Yes	3	No
20	Male	22	24	29	1	4	2	2	2	3	3	Yes	3	No
21	Female	56	56	59	1	2	3	2	3	2	2	Worsening	0	No
22	Male	53	53	55	1	5	3	5	3	2	3	No	0	No
23	Male	46	46	59	1	7	3	7	1	2	2	Yes	1.5	No
24	Male	19	34	36	1	4	3	4	2	1	1	Yes	3	No

*A score of 1 is mild, a score of 2 is moderate, and a score of 3 is severe.

Continues

Table 2. Continued

Patient Number	Sex	Onset Headache Age (Years)	Chronification Headache Age	First Treatment Age (Years)	Treatment Number	Daily Number of Attacks Pretreatment	Intensity of Attacks Pretreatment*	Daily Number of Attacks Posttreatment	Intensity of Attacks Posttreatment*	Number of Drugs Pretreatment	Number of Drugs Posttreatment	Improvement	Improvement Length (Months)	Asymptomatic
Radiofrequency ablation														
1	Male	26	27	43	1	1	3	1	3	3	3	No	0	No
2	Male	19	21	26	1	1	2	0.07	2	7	3	Yes	136	Yes
3	Male	23	26	27	1	6	3	4	2	4	4	Yes	1	No
4	Male	40	42	46	1	2	3	1	2	3	3	No	0	No
5	Male	24	24	28	1	1	3	0.28	3	2	0	Yes	7	No
					2	0.57	3	0.14	2	0	0	Yes	5	No
6	Male	16	37	42	1	3	3	1	2	2	2	Yes	10	No
					2	4	3	0.14	1	2	2	Yes	10	No
7	Male	34	36	48	1	7	1	7	1	2	1	No	0	No
8	Male	35	44	46	1	3	3	3	3	2	2	Yes	1	No
9	Male	20	20	33	1	3	3	0	3	1	0	Yes	13	No
10	Female	38	42	44	1	12	3	12	3	1	0	No	0	No
11	Female	37	37	43	1	1	3	0.42	2	2	1	Yes	1.5	No
12	Female	30	32	36	1	4	2	2	2	1	1	Yes	3	No
13	Female	46	46	48	1	8	3	8	3	4	4	No	0	No

*A score of 1 is mild, a score of 2 is moderate, and a score of 3 is severe.

Table 3. Available Studies on Sphenopalatine Ganglion Radiofrequency for Chronic Cluster Headache

Study	Number of Patients	RF Modality	Technique	Age (Years)	M:F	Frequency Pretreatment (24 hours)	Intensity Pretreatment	Frequency Posttreatment (24 hours)	Intensity Posttreatment	Complications	Headache Length (Years)	Partial Improvement (%)	Complete Improvement (%)	No Improvement (%)	Follow-Up (Months)
Sanders and Zuurmond, 1997[13]	10 CCH 56 ECH	RFA	70°C 60 seconds	33.6 ± 5.5	8:2	3.4 ±1.3	NDA	2.3 ± 0.6	NDA	Epistaxis (n = 8) Cheek hematoma (n = 11) Maxillary nerve lesions (n = 4) Temporary palate hypesthesia (n = 9)	26.4 ± 13.2	30	30	40	24 ± 9.7 (12—70)
Filippini-de Moor et al., 1999[12]	2 CCH 17 ECH	RFA	80°C 60 seconds	47.2 (19—76)	18:1	NDA	NDA	NDA	NDA	No	11.6 (2—38)	100	0	0	33 (9—64)
Chua et al., 2011[15]	2 CCH 1 ECH	PRF	45 V 42°C	62 (52—72)	0:2	0.28	8	2	7	No	22.5 (10—35)	50	50	0	4
Narouze et al., 2009[11]	15 CCH	RFA	80°C 60 seconds	NDA	NDA	2.43	8.6	1.18	4.2	Temporary Paresthesia (n = 7) Permanent anesthesia (n = 1)	NDA	46.7	20	33.3	18—24
Bendersky et al., 2015[16]	3 CCH	PRF RFA	45 V 42°C 120 seconds; 80° 90 seconds	42 (36—53)	1:2	3.66	10	2.66 (PRF)	8.33	No	8.66	0	100 (RFA)	0	9.6
Fang et al., 2016[10]	3 CCH 13 ECH	PRF	42°C 120 seconds	48.0 ± 15.9	3:0	2.0 ± 1.7	8.6	NDA	NDA	No	20.0 ± 14.1	0	1	2	17.0 ± 5 (12—30)
Loomba et al., 2016[17]	1 CCH	RFA	80° 60 seconds	30	1	Daily	3	NDA	NDA	No	2.5	100	0	0	10
Current study	37 CCH	PRF RFA	40 V 42°C 120 seconds; 80° 60 seconds	40 (26—59)	29:8	3.66 (0.3—12)	2.76	2.56 (0—12)	2.08	No	9.8 (2—38)	56.70	13.5	29.70	68.1 (15—148)

RF, radiofrequency; M, male; F, female; CCH, chronic cluster headache; ECH, episodic cluster headache; RFA, radiofrequency ablation; NDA, no data available; PRF, pulsed radiofrequency.

The mean effectiveness period was slightly higher with RFA (5.21 months) than with PRF (4.69 months) ($P = 0.820$). However, it has been objectified that the passage of time tends to decrease the efficacy of both techniques ($P < 0.001$).

RFA was repeated in 2 patients and PRF was repeated in 5 patients because the CH recurred after the initial improvement or because there was no improvement and they agreed to make a second attempt.

In those patients in whom the procedure was repeated, the Cohen κ method showed a percentage of agreement between the response to the first and second treatment of 100%, and the κ (concordance coefficient) obtained was 1 (which translates into a probability that the results are random to very low chance). The intensity and frequency of the attacks did not show differences between the first and second treatments ($P = 0.99$ and $P = 0.88$, respectively). Therefore, in all cases in which there was no improvement after the first treatment, it was not observed after the second treatment, and in those cases where partial transient improvement was initially observed, it also resulted in partial transient improvement after the second attempt.

DISCUSSION

Our results showed that radiofrequency of the SPG is a safe and partially effective method to treat CCHr. After a mean follow-up period of 68 months, we did not record any adverse effects related to the procedure.

Despite that in our series the percentage of patients who presented clinical transient improvement and also the percentage of asymptomatic patients after PRF was slightly higher than after RFA, the difference was not statistically significant.

Only 5 cases in which the symptoms disappeared indefinitely were achieved after the first interventional procedure. None of the remaining patients remained asymptomatic despite the different neuroablative/neuromodulatory techniques and the multiple combinations of treatment used. However, further studies are needed to assess if the response to the first treatment is a prognostic factor (13.5%; 95% confidence interval, 4.5%–28.8%).

Radiofrequency of the SPG, both thermal and pulsed, is an older procedure which has been relegated in many centers by the novel techniques of neuromodulation. However, it is a method associated with few complications, and despite the fact that in most patients it offers transient relief, in some cases the objective improvement has been permanent. Radiofrequency lesions have been shown to be more successful than other invasive approaches, such as techniques focusing on the trigeminal nerve.[10,14] **Table 3** shows the cases of CCHr treated by radiofrequency, both thermal and pulsed, published to date.[10-13,15-17] Our results agree with one of the published series; however, the results in the literature are very variable depending on the series.

Although RFA has been shown to be effective in short series with CCHr, the results of the published series are worse than in cases of episodic headache. In fact, Sanders and Zuurmond[13] reported that 60.7% of the 56 patients with episodic CH and 30% of the 10 patients with CCHr achieved complete pain relief after RFA.

Most patients with episodic CH can be effectively treated with medication. Invasive therapy has traditionally been reserved for drug-resistant cases or severe chronic headaches. Several non-pharmacologic invasive methods have been used over the years.[14,18] Regarding the SPG, attempts of cryosurgery, radiosurgery, gamma knife, and even ganglion resection are worth mentioning.[19-21] The methods based on the injection of substances, currently consisting of blocks with local anesthetics and corticosteroids, result in a partial relief of pain with a high rate of recurrence.[22]

Neuromodulation techniques for the treatment of CH are on the rise.[6,23,24] These include deep brain stimulation of the ventroposterior hypothalamus; however, we must take into account that it is a procedure with potentially fatal complications, with intracerebral hemorrhages and even death having been reported.[5,25] Less invasive and risky methods, such as stimulation of the occipital nerve or stimulation of the SPG, are also being used with variable results. However, these are techniques that carry a high economic cost and varying efficiency rates.[26,27] Because of the implanted prosthetic material, we have to add to the complications the increase in infection rates, hardware-related complications, the need for battery replacement, disconnections, and ruptures of the system.[28,29]

SPG radiofrequency complications documented in the literature include the following[9,13,30]: hypoesthesia of the palate, resulting from damage of the major superficial petrosal nerve, which is usually transient; epistaxis; infection associated with the puncture; facial hematoma because of damage to the maxillary artery or pterygoid plexus; hypersensitivity or dysesthesias on the palate, jaws, cheek, or posterior pharynx; maxillary hyperpathia, a consequence of the partial peripheral lesion of the third branch of the trigeminal nerve, considered as deafferentation pain; dry eye; and reflex bradycardia during the lesion.

However, in the 37 patients treated in our center, we did not see any adverse effects after a mean follow-up period of 68 months. We consider, in agreement with the literature, that a thorough positioning of the electrode combined with a sensory test at 50 Hz of the location, prior to radiofrequency, can reduce the incidence of these adverse effects. Unlike RFA, PRF is thought to produce its effect by creating high-intensity electric fields without inducing a relevant injury to the neural tissue surrounding the tip of the electrode. Therefore, the incidence of these complications would theoretically be reduced in the case of PRF.

In all the patients, the technique was performed as an ambulatory procedure. This fact has a strong economic impact because it is a technique that does not require hospitalization or general anesthesia, a factor to consider if we compare it with other invasive treatments (e.g., neuromodulation techniques).

Because of the higher rate of complications that have been described in the literature related to RFA, and because in our series the effectiveness of PRF and RFA is similar, in our current clinical practice we consider PRF as the first invasive therapeutic option in those patients in whom drug therapy has failed.

CONCLUSIONS

SPG radiofrequency is a quick, partially effective, economic, and safe method with a low level of complications. Because of these

characteristics, this technique must be taken into consideration in relation to other invasive treatments with a greater number of complications and economic cost to treat CCHr.

There are no statistical differences between RFA and PRF. Because of the similarity in efficacy and the greater theoretical risk of thermal complications, we recommend the use of the pulsed mode.

Prospective studies with a greater number of patients are required to objectify the efficacy and real effectiveness of SPG radiofrequency to be able to assess definitive conclusions.

ACKNOWLEDGMENTS

The authors thank Dr. Ignasi Gich for his contribution to the statistical analysis of the manuscript.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 29 August 2018; accepted 1 October 2018

Citation: World Neurosurg. (2019) 122:e262-e269.
https://doi.org/10.1016/j.wneu.2018.10.007

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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1878-8750/$ - see front matter