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Results of sphenopalatine ganglion pulsed radio-frequency treatment in patients suffering from episodic cluster headache

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Abstract

Background & Objective: The aim of this study was to investigate the short- to medium-term effects of pulsed radiofrequency (PRF) of the sphenopalatine ganglion on episodic cluster headache. Methods: This is a retrospective observational study, 26 patients who underwent PRF of the sphenopalatine ganglion were retrospectively evaluated. The Visual Analogue Scale (VAS) score, number of headache attacks per week, autonomic symptoms and medication use were recorded at 1, 3 and 6 months after the procedure. *Results:* The mean VAS scores were significantly lower at the 1-, 3-, and 6-month evaluations compared with pre-procedure values ($P < 0.001$). At the 6th month after the procedure, the proportion of subjects who completely stopped using medications was 26.9%, and the proportion with a decrease in autonomic symptoms was 61.5%. No complications were encountered as a result of the procedure.
Conclusion: The application of PRF to the sphenopalatine ganglion is an effective and safe treatment option for episodic cluster headache in the short to medium term.

Keywords: Cluster headache, pain management, sphenopalatine ganglion, pulsed radiofrequency

INTRODUCTION

Cluster headache (CH) is the most common type of trigeminal autonomic cephalalgia. According to the diagnostic criteria of the third edition of the International Classification of Headache Disorders (ICHD-3), CH is characterized by episodic unilateral headache attacks lasting 15–180 minutes with associated ipsilateral autonomic symptoms.[1] The latter symptoms include the following: ptosis ipsilateral to the headache, miosis, conjunctival lacrimation, nasal congestion, rhinorrhea, eyelid edema, as well as forehead and facial sweating. The diagnosis of CH is made based on the patient's case history.

The prevalence of CH has been estimated to be between 0.5 and 1 per 1000 individuals.[2] The fact that it is a relatively rare disease makes research into its diagnosis and treatment difficult. It is one of the most severe headaches and has been called "suicide headache". Therefore, early diagnosis and treatment are critical.

The sphenopalatine ganglion (SPG), also known as the pterygopalatine ganglion or Meckel's ganglion, is an extracranial parasympathetic ganglion situated in the pterygopalatine fossa. Sympathetic, parasympathetic, and sensory neurons are present in the SPG.[3] The SPG is thought to have a pivotal role in cluster headache even though the pathophysiology of CH is unknown. CH may be divided into episodic and chronic forms. Episodic cluster headaches (ECH) last from 1 week to 1 year, with remissions of at least 1 month in between. Chronic cluster headache (CCH) persists for more than one year without remission or when remissions last less than 1 month. ECH comprises approximately 80%–90% of CH cases.[4]

There is no cure for CH, and pharmacological therapies are the first line of treatment. Nonetheless, owing to the limited efficacy and the side effects of pharmacological therapy, invasive methods such as nerve blocks, neurolytic procedures, and surgical procedures have been employed.[5] Radiofrequency (RF) therapy to the SPG has been tried in patients who remain unresponsive to conservative treatments.

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However, only a limited number of studies have investigated the efficacy of this intervention. Continuous radiofrequency (CRF) ablation and pulsed radiofrequency (PRF) are the two forms of RF therapy. High temperatures (60°C–80°C) from high frequency alternating currents are used to induce the formation of tissue necrosis in CRF. On the other hand, in PRF, short pulses of 20 milliseconds are used every 0.5 seconds. The tissue cools in between pulses, and tissue temperature does not exceed 42°C (6), resulting in minimal tissue damage. While this is the most significant benefit of PRF, PRF is generally inferior to CRF in terms of success of pain relief.[5] The goal of this study was to investigate the efficacy and safety of SPG-PRF treatment in 26 patients with ECH.

METHODS

The present study was carried out in the Department of Algology at Ankara University Faculty of Medicine after approval was obtained from the local ethics committee (reference number: i5-331-21).

The data of 36 patients who received SPG-PRF treatment between January 2015 and January 2020 were retrospectively examined by reviewing patient file records obtained through telephone or face-to-face interviews. Inclusion criteria were: diagnosis of ECH based on the ICHD-3 criteria, resistance to conventional treatments (pharmacological therapy, greater and lesser occipital as well as trigeminal blocks), severe attacks (VAS value of 7 or higher) in the 6-month period before the procedure. All subjects demonstrated a temporary therapeutic response (more than 50% reduction in pain scores) to transnasal topical SPG block (a cotton-tipped applicator with 2% lidocaine was advanced into the nares parallel to the zygoma with the tip angled laterally until it rested for 30 minutes on the nasopharyngeal mucosa posterior to the middle nasal turbinate). Exclusion criteria were: a psychiatric disorder or abnormal brain computed tomography or magnetic resonance imaging. Seven of the initial subjects were excluded from the study due to different diagnoses, and three others were excluded owing to incomplete patient records. The final study group comprised 26 patients.

The PRF was performed as an outpatient intervention by the same physician in operating room conditions with standard monitoring (electrocardiogram, pulse oximetry and non-invasive arterial blood pressure) under sedation with 0.05 mg/kg i.v midazolam. An infrazygomatic approach was used. The patient was positioned supine on the operating table, with the head fixed with supports to prevent movement. A peripheral venous line was placed. The pterygopalatine fossa, which has the appearance of an inverted pyramid, was visualised using a C-arm fluoroscopy device. The mandibular notch served as the entry point of the needle into the skin (Figure 1A). This point was marked, and 1% lidocaine was injected into the skin. A 10-cm-long 22-gauge needle with a 5-mm straight active tip was used for RF. The RF needle was advanced medially and superiorly to the pterygopalatine fossa. To control the depth of insertion, an anterior-posterior fluroscopic view was used, and the needle tip was advanced until it was just lateral to the nasal wall at the level of the middle turbinate (Figure 1B). The RF electrode was then used to replace the needle guide. A 50 Hz stimulus with a pulse width of 0.25–0.5 milliseconds was delivered. At a preliminary stimuluis of 0.5–0.7 V, subjects would experience paresthesia (tingling sensation and/or dysesthesia) endonasally at the top of the nose. To prevent trigeminal contact from generating mandibular contraction, motor stimulation at a frequency of 2 Hz was used. To rule out intravascular spread and establish that the needle tip was within the pterygopalatine fossa, 0.2 mL contrast was administered after the final needle positioning. Dispersion of the contrast material was confirmed using fluoroscopy. After obtaining the correct final position, 0.5% bupivacaine was used for local anesthesia. Two rounds of 42°C and 40V PRF were applied for 120 seconds.

For all patients, pre-procedural demographic information, age at onset of CH, and the side of head pain were documented. The frequency and intensity of attacks as well as pain-free intervals before and after SPG PRF treatment, the requirement for analgesics, and the duration of pain-free intervals were recorded. The primary objective of this study was to determine short- and medium-term reduction in pain intensity with SPG-PRF treatment. The secondary objective was to determine the short- and medium-term reduction in patients' autonomic symptoms and medication use. For this purpose, the parameters listed below were utilized to evaluate patients pre-procedure and at 1, 3, and 6 months after SPG-PRF.

Pain intensity was assessed using a 10 cm visual analog scale (VAS). Adequate analgesia was defined as a 50% drop in the VAS score relative to the pre-procedure value. The impact of

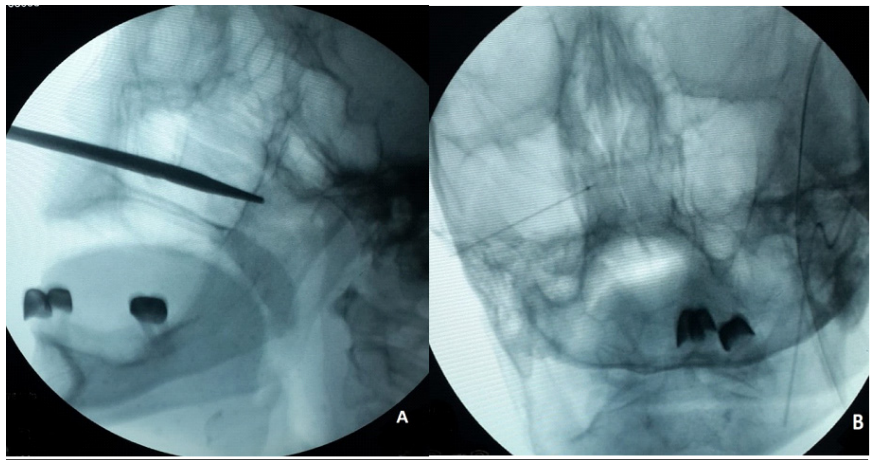

Figure 1. A: C-arm-guided sphenopalatine ganglion radiofrequency- Lateral view showing the entry point (mandibular notch) of the needle into the skin. B: Anteroposterior view showing needle tip terminating immediately lateral to ipsilateral nasal wall. These images were selected from the authors' archives.

treatment on medication use was assessed using a three-point scale (1: unchanged, 2: decreased, 3: medication discontinued). The number of headache attacks per week were documented before and after the procedure. Since ECH patients have variable pain-free intervals between cluster periods, post-procedure results at months 1 and 3 were considered short-term treatment outcomes, and the 6-month result was considered a medium-term treatment outcome.

Cessation of all medications and a VAS of 0 was defined as a complete response (CR). A decrease in the VAS score and requirement for medications was defined as a partial response (PR). Absence of a decrease in the VAS score and medication use was defined as no response (NR). The extent of autonomic symptoms was determined and categorized as absent, present, or decreased. Subjects were observed for complications such as epistaxis, hematoma, diplopia, hypoesthesia, and muscle weakness.

Statistical analysis was performed using the SPSS Version 23.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). Nominal variables were reported as percentages and compared with a two-tailed Chi-square or Fisher test as applicable. A two-tailed Shapiro–Wilk test was used to examine whether the continuous quantitative variables followed a Gaussian distribution. Continuous quantitative variables were reported and represented as medians (min-max). The Wilcoxon signed-rank test was used to compare the medians of two related groups. P values less than or equal to 5% were considered significant

RESULTS

The demographic and clinical characteristics of the 26 patients (17 [65.3%] male and nine [34.6%] female) included in the study are presented in Table 1.

The patients' mean VAS score was 8 before the procedure and 4 at one month, 5 at three months, and 6 at six months following the procedure. Table 2 shows these results. The mean VAS scores before the procedure were significantly lower ($p < 0.05$) at 1, 3, and 6 months after the procedure. It is noteworthy that VAS scores tended to increase again after month 3. (Figure 2). Pre- and post-procedure, changes in the duration of clusters and attack-free periods were found to be statistically different in the 6-month follow-up period (Table 3). The mean attack frequency was 15/week before the procedure. After the procedure, it decreased to 8/week at month 1, 9/week at month 3, and 10/week at month 6.

Table 1: Demographic and clinical characteristics of the patients

Variables	
Age (year)	34 (25-52)
Sex	
Male	17 (65.4%)
Female	9 (34.6%)
Side	
Right	17 (65.4%)
Left	9 (34.6%)
Duration of pain (year)	2,5 (1-9)

Table 2: Mean (±SD), median, minimum, and maximum VAS scores at different follow-up times

	n	Mean±SD	Medyan	Minimum	Maximum
Before the procedure*ϕθ	26	8,4±0,809	8	7	10
1. month*	26	4,3±2,729	4	0	9
3. month ϕ	26	4,8±3,124	5	0	10
6. month θ	26	5,2±3,266	6	0	10

* The difference between the baseline and month 1 is statistically significant (P < 0.001).
ϕ The difference between the baseline and month 3 is istatistically significant (P < 0.001).
θ The difference between baseline and month 6 is statistically significant (P < 0.001).

The number of patients whose VAS score decreased by more than 50% one month after the procedure was 18 (69,2%), but by month 3, this had dropped to 11 (42,3%). Seven patients (26.9%) had a CR six months after the procedure, while four patients (15.4%) had a PR. There were 15 patients in the group without a response (57.7%). A patient whose VAS score did not change but whose dose of drugs decreased due to drug-related side effects was included in the latter group. After the procedure, 18 (69.2%) patients had absent or reduced autonomic symptoms at months 1 and 3, and 16 (61.5%) had improved autonomic symptoms at month 6.

Three of the seven patients (two at the ninth month and one at the 11th month) had a relapse of cluster episodes requiring repeated PRF in the six-month follow-up period. In two of these three patients, the pain completely disappeared, and in one, the pain was reduced by 70%. The procedure was repeated in two of the six patients whose VAS score did not change in the first month after the procedure, However,in thesse 2 cases there was no decrease in their pain following the second procedure.

No major side effects or complications developed as a result of SPG-PRF treatment.

DISCUSSION

This study shows that administering PRF to patients with ECH can alleviate pain and autonomic symptoms in the short and medium term without causing any complications or side effects. In our study, a statistically significant decrease in cluster duration and VAS scores and an increase in attack-free periods was found in the 6-month follow-up of the patients with SPG PRF treatment before and after the procedure. Several studies exploring the efficiency of various RF modalities in CH have been published since the first report of application of RF to the SPG.[7-14]

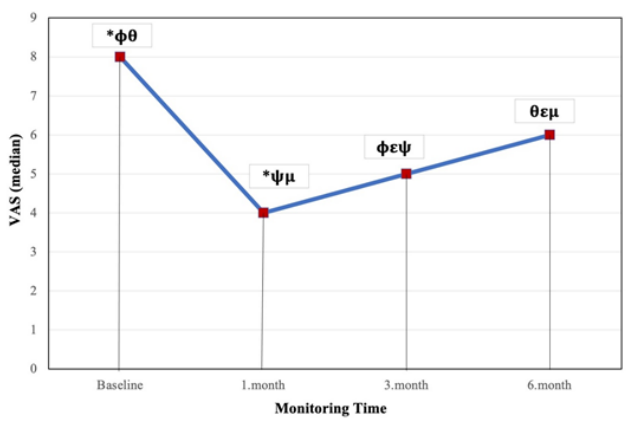

Figure 2. Graphic for the change in VAS scores at different follow-up times.
* Difference between baseline and month 1 is statistically significant (P < 0.001).
ϕ Difference between baseline and month 3 is statistically significant (P < 0.001).
θ Difference between baseline and month 6 is statistically significant (P < 0.001).
ψ Difference between month 1 and month 3 is not statistically significant (p=0.291).
ε Difference between month 3 and month 6 is statistically significant (p=0.027).
μ Difference between month 1 and month 6 is statistically significant (p=0.019).

Table 3: Variation in duration of cluster and attack-free periods of episodic CH patients' response to PRF at follow-up

Follow-up time point	**Pre-operation** (mean±sd)	**Post-operation** (6 months) (mean±sd)
Duration of clusters (minute)	92.69±26.47	57.69±43.20*
Duration of attack-free (day)	95.19±35.48	116.54±46.62*

PRF- pulsed radiofrequency; CH – cluster headache; sd-standart deviation; *p < 0.05 vs. pre-operation.

Chua *et al*. were the first to use SPG-PRF on three patients with CH who were resistant to conservative treatments.[10] They reported total pain alleviation in two patients and partial pain alleviation in one patient four months following PRF, with no neurological side effects or complications. Frang *et al*. reported that 11 (85%) of 13 patients with ECH and 1 (33%) of three patients with CCH completely recovered from headaches after treatment in an average of 6.3 ± 6.0 days.[11] The higher success rate in both studies compared to our study may be related to the shorter follow-up period of the patients. Neither study, however, demonstrated long-term results of PRF for CHs with a large-scale cohort. The authors of these studies noted that their results needed to be interpreted in the light of the fact that CH is characterized by spontaneous regressions. To the best of our knowledge, our study is the largest to date of SPG PRF therapy in ECH patients.

By month 6, 26.9% (7 people) of the patients in our study had achieved CR. This finding is consistent with the study of Chen *et al*., who advocated the use of SPG-PRF for CH in 2019.[9] They reported that 22.2% of 45 ECH patients recovered completely following PRF treatment. In their study, PRF was performed under computed tomography (CT) guidance. We believe that our use of fluoroscopy and a localizing stimulus to determine the optimum stimulation site is sufficient to substitute for CT guidance. The latter also involves disadvantages of radiation exposure and higher cost. Akbas *et al*. evaluated 27 patients treated with PRF.[7] Their results showed that 35% of the patients experienced complete pain relief, 42% had moderate relief, and the other 23% had no relief. The participants in this study included patients suffering from chronic head and facial pains of various etiologies, such as autonomic cephalgia, atypical facial pain, SPG neuralgia due to postherpetic neuralgia, atypical TN unresponsive to previous treatments, and unilateral migraine headaches. In a similar study, Bayer *et al*. found that 65% of 30 patients with chronic head and facial pain who received SPG-PRF treatment experienced mild to moderate relief during a follow-up period of 4–52 months.[8] These studies indicate that SPG PRF shows promise in the treatment of many types of headache and facial pain. In both studies, the success rate of PRF was higher than our study. This may be because of the diverse etiologies treated. There are also studies reporting the results of CRF and PRF treatment in CCH. A prospective study by Salgado-Lo'pez *et al*. investigated the usefulness of either RFA or PRF in refractory CCH.[13] Twenty-four patients received PRF, and 13 patients received CRF. Five patients (13.5%) experienced complete clinical relief in both pain and autonomic symptoms, 21 patients (56.8%) experienced partial and temporary relief, and 11 patients (29.7%) had no improvement. PRF and CRF were equally effective. There is no consensus on which RF modality to use in CH. Narouze *et al*. found that approximately 50% (7/15) of the patients with CCH experienced temporary paresthesia in the upper gums and cheek lasting 3 to 6 weeks afterwards. One patient developed a permanent coin-shaped area of anesthesia on the cheek.[12] Although SPG-CRF treatment has not been linked to major side effects in published literature, in our clinic, we prefer PRF because of the potentially greater destructive effects of CRF and the lack of documented difference in effectiveness between PRF and CRF in CH. In our study the mean VAS scores of the patients decreased in the 1st month after the procedure, but this decrease lessened significantly at by the 3rd month afterwards,. Chen *et al*. reported that patients with ECH experienced their first recurrence within in the nine month period following PRF.[9] Salgado Lopez *et al*. reported the mean time to recurrence of pain after PRF as 4.69 months.[13] PRF was repeated in 5 patients who had pain recurrence who were unresponsive to treatment. The responses to the first and second treatments in these patients were 100% consistent. The mechanism of PRF activity in chronic pain is still unknown. Changes in the gene expression of pain-producing neurons have a neuromodulatory effect via PRF.[15] This neuromodulatory effect on the nerve tissue may fade over time, and pain is

likely to return. It is still impossible to predict which patients may relapse following PRF treatment and when this may occur. However, our experience and published literature sugggests that individual response (CR or NR) after the initial PRF treatment predicts effectiveness of subsequent PRF treatments, based on the limited data in our study and the literature.

On March 11, 2020, the World Health Organization declared a novel coronavirus (COVID-19) outbreak a pandemic.[16] As a result, elective surgeries and patient examinations were postponed or restricted, and many medical personnel including pain therapists focused on managing COVID-19 patients. SPG-PRF procedures were conducted on all patients in our study before the COVID-19 outbreak began. However, in the last months of 2019, we noticed that there was a reduction in follow-up visits of the patients we treated. As a result, our follow-up duration was reduced by half. Although the COVID-19 pandemic disrupted the healthcare system, one of the most important lessons it taught us was the importance of treating patients with iontractable chronic pain with 'one-shot' treatments such as RF in order minimize hospital attendances.

This study has several limitations. First, the results are from a single center. Second, it is retrospective. There was no control group and we could not extend our follow-up duration beyond 6 months.

In conclusion, SPG-PRF treatment is a safe and effective analgesic approach that reduces pain and medication use in the short and medium term while avoiding major side effects or complications. Further studies are required to determine the efficacy and safety of SPG-PRF treatment, as well as to determine optimum procedural protocols and algorithms for this indication.

DİSCLOSURE

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Conflict of interest: None

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