Acta Neurologica Belgica (2019) 119:601–605
https://doi.org/10.1007/s13760-019-01203-6

ORIGINAL ARTICLE

Safety and efficacy of percutaneous pulsed radiofrequency treatment at the C1–C2 level in chronic cluster headache: a retrospective analysis of 21 cases

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Received: 12 March 2019 / Accepted: 20 August 2019 / Published online: 3 September 2019

Abstract
We performed a study of the safety and efficacy of percutaneous pulsed radiofrequency (PRF) treatment directed at C1 and C2 levels as performed at our local pain clinic in refractory chronic cluster headache (CCH) patients. We identified 21 CCH patients treated with PRF (240 s, max. 45 V, max. 42 °C) directed at the ganglion and/or nerve root of C1 and C2. Data were collected through retrospective analysis of patients' files and include demographic variables, onset and duration of the headache, mean attack frequency, and prior pharmacological treatment. Safety and reduction of attack frequency in the first 3 months after a first PRF treatment was the primary outcome parameter of this study. All patients had been treated with at least two prophylactic drugs and 19 (90%) had previously been treated with verapamil, lithium, and topiramate. Ten patients (47.6%) reported no meaningful effect, four patients (19%) reported a meaningful reduction of < 50%, and seven patients (33.3%) reported a reduction in headache burden of at least 50% in the 3 months following treatment. Two patients reported occurrence or increase in frequency of contralateral cluster attacks. No other adverse events were reported or detected at follow-up. Upper cervical PRF treatment appears to be a safe procedure that could prove effective in the treatment of patients with refractory CCH and warrants a prospective study.

Keywords Cluster headache · Retrospective study · Pulsed radiofrequency treatment · Interventional management · Refractory headache

Introduction

The three branches of the trigeminal nerve transmit afferent sensory and nociceptive information of the face, the anterior part of the head, and the anterior as well as middle cranial fossa. The cutaneous and deep structures of the back of the head and upper neck are innervated by the greater occipital nerve (GON), the lesser occipital nerve (LON), and the third occipital nerve which project centrally through the upper cervical nerves and dorsal roots [1]. Patients with primary headaches not only report pain from the anterior part of the head innervated by the trigeminal nerve, but also from the back of the head and neck innervated by the upper cervical roots [2]. In the last three decades, through several animal model experiments [3–5], the concept emerged of a trigeminocervical complex, a functional entity that acts as a major relay for convergent nociceptive afferent input from the supratentorial meninges (innervated by the trigeminal nerve) and cervical structures (innervated mainly by the GON) [2, 3]. It is hypothesized that through this trigeminocervical complex input from the upper cervical nerves can modulate trigeminal nociceptive input [6]. The importance of relay neurons of the trigeminocervical complex in primary headache disorders is the theoretical framework that led to the development of modalities of neuromodulation directed at the afferent input of the upper cervical spine as a means of modifying the disease course of primary headache disorders. The treatment techniques tested so far in cluster headache are greater occipital nerve infiltration [7, 8], occipital nerve stimulation [9–11] and upper cervical spinal cord stimulation [12]. Thus far, no studies have reported

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on radiofrequency ablation or pulsed radiofrequency (PRF) treatment directed at upper cervical neural structures.

Radiofrequency ablation is a destructive technique that allows to make well-circumscribed lesions by heating the neural tissue adjacent to the uninsulated tip of the electrode. Contrary to the use of continuous radiofrequency signal in radiofrequency ablation, in PRF, treatment pulses of radiofrequency signal are administered and the temperature is kept in a non-destructive range. Its main advantages are less pain during the procedure and a lower risk of motor deficits and deafferentiation pain. On electron microscopic analysis, some ultrastructural changes such as an increased numbers of vacuoles and enlarged endoplasmic reticulum cisterns are seen after PRF stimulation, but the mechanism of action of PRF remains largely unknown [13, 14].

There has been some interest in using the PRF technique for cluster headache patients and a few case series of PRF interventions directed at the pterygopalatine ganglion have been published (the largest series reported the results in 16 patients) [15–18]. Studies on PRF treatment directed at the trigeminal ganglion are lacking, but limited retrospective data on radiofrequency ablation of this structure are available [19].

In this report, we present the results from a study that we conducted on the safety and effectiveness of percutaneous PRF treatment directed at the C1 and C2 levels in chronic cluster headache (CCH) patients at our pain clinic.

Methods

This study was approved by our institutional ethical review board. Informed consent was not required for this retrospective clinical study.

Data collection

A retrospective chart review of patients' medical records was performed of all cluster headache patients who underwent the procedure at the Pain Clinic of the Ghent University Hospital between January 2010 and August 2017. We predefined variables we expected to be consistently available in the medical records including demographic variables, onset and duration of the headache, mean attack frequency at baseline, medication history, medication at baseline and medication changes, previous interventional procedures, and adverse events.

Description of the procedure

The treating physician at the pain clinic informed all patients properly about the empirical nature of this treatment. Written informed consent was obtained from all patients prior to the procedure. The PRF application is performed under fluoroscopic guidance. The patient is supine. The C-arm image intensifier is positioned with the intensifier facing the side being treated. It is extremely important to achieve perfect superimposition of both sides of the C1 and C2 vertebrae. The entry point for C1 is at the junction of the upper 2/3 and lower 1/3 of the bony pillar of C1. A 22G 50 mm RF needle is inserted and advanced using tunnel vision (a view where the RF needle is coaxial to the X-rays) until it is firmly gripped by the superficial tissues. The position of the needle is checked in the antero-posterior axis while identifying the lateral margin of the atlanto-axial joint. The needle is advanced to the lateral border of the atlanto-axial joint. At this point, the proximity to the ganglion/nerve is confirmed using sensory (50 Hz) and motor (2 Hz) stimulation at a level of 0.5 V or less. If necessary, the needle is advanced further, but may never be deeper than the lateral 1/4 of the atlanto-axial joint. The entry point for C2 lies at the junction of the upper 1/3 and lower 2/3 of the bony pillar of C2. A 22G 50 mm RF needle is inserted and advanced using tunnel vision until contact with bone at the target point. After bony contact, the needle is angled cranially into the center of the C2 space at the same depth as the bony target. The position of the needle is checked in the antero-posterior axis. At this point, the proximity to the ganglion is confirmed using sensory (50 Hz) and motor (2 Hz) stimulation at a level of 0.5 V or less. If necessary, the needle is advanced, but may never be deeper than the lateral 1/3 of the atlanto-axial joint. Finally, the radiofrequency pulse is administered at max. 45 V for 240 s maintaining the temperature below 42 °C.

Results

Subjects

Twenty-one subjects were treated between 2010 and 2017. All patients were referred through our headache clinic and matched the diagnostic criteria for CCH (ICHD-III code 3.1.2) [20]. The age of patients ranged from 23 to 62 years with a median age of 50 years. The median duration of CCH prior to PRF treatment was 5 years with a range of less than a year up to 33 years. All patients had tried at least two prophylactic drugs prior to PRF treatment; all had been on an adequate dose of verapamil, 19 out of 21 on lithium, 19 on topiramate, 11 on gabapentin, 10 on methysergide (which is currently no longer available in Belgium), 10 on melatonin, and 9 on valproate. One patient had a failed trial with occipital nerve stimulation after which the leads were removed. One patient was implanted with an occipital nerve stimulator 7 weeks after PRF treatment and before evaluation at our service. Two patients had a stimulator at the pterygopalatine ganglion. Seven patients had previously undergone PRF

treatment directed to a different structure: six patients of the pterygopalatine ganglion, one patient of the Gasserian ganglion, and one patient (who had also undergone PRF treatment directed to the pterygopalatine ganglion) of the stellate ganglion.

Efficacy

The results regarding efficacy are summarized in Table 1, along with the self-reported frequency at baseline and the numbers of years suffering from CCH. Ten patients (47.6%) reported no meaningful effect after PRF treatment, four patients (19%) reported a meaningful reduction in headache burden of < 50% and seven patients (33.3%) reported a reduction in headache burden of more than 50% in the 3 months following treatment. Changes in prophylactic cluster treatment occurred in seven patients in the first 3 months of follow-up and of these three patients reported a reduction in headache burden of more than 50%. In one out of three medication was reduced; this patient reduced the daily dose of verapamil from 720 to 480 mg because of intolerability. In one patient on a combination therapy of topiramate/verapamil/melatonin/valproate, the daily dose of valproate was increased from 1000 to 2000 mg. One patient switched from lithium, topiramate, and corticosteroids to gabapentin and long-acting opioids.

Adverse events

One patient with unilateral attacks on both sides of the face received PRF on the preponderant side and experienced more than 50% reduction in headache burden ipsilateral to the procedure, but reported an increase in contralateral attacks. A subsequent PRF treatment directed at the C1–C2 level on this contralateral side had no effect. One other patient with strictly unilateral attacks at baseline and a complete resolution of cluster attacks after ipsilateral PRF treatment reported recurrence of contralateral cluster attacks 11 months after the procedure. No additional adverse events (including bleeding, infection, or neuropathic pain) were detected at regular follow-up.

Discussion

We report on a technique that originated in our local pain clinic. The treating physician at the pain clinic felt it to be a reasonable and potentially less invasive treatment target alternative to a sphenopalatine ganglion intervention. There are some limitations to our study which is based on retrospective and uncontrolled data; although the necessary relevant data were consistently available in the patients' files, there was no standardized way of reporting. The patients' prophylactic medication changed

Table 1 Overview of results in our patient group

N	Years chronic	Attack frequency at baseline (per day unless specified)	Patients' estimate of % change in the 3 months after procedure
1	7	8	Some effect, < 50%
2	16	< 1/week	None
3	33	6	More than 50% reduction in ipsilateral attacks
4	10	1 to 2	More than 50% reduction
5	22	1	None
6	5	3 to 4	More than 50% reduction
7	1	0 to 5	More than 50% reduction
8	15	8	More than 50% reduction
9	2	2 to 3	None
10	7	3	Some effect, < 50%
11	1	5	None
12	1	7 to 8	None
13	7	2 to 3	None
14	2	6 to 7	More than 50% reduction
15	3	2 to 3	None
16	2	1 to 5	None
17	2	1 to 2	Some effect, < 50% reduction
18	2	4	None
19	12	4 to 5	None
20	7	3 to 4	More than 50% reduction
21	3	5 to 10	Some effect, < 50% reduction

during the assessment period in a significant proportion of patients. Therefore, this analysis provides only preliminary data regarding the efficacy of PRF treatment at the C1–C2 level and does not allow comparison to other available interventional treatments. The number of patients treated is small; however, the size of this consecutive case series is comparable to other invasive and non-invasive neuromodulation studies in patients with cluster headache.

A global improvement of at least 50% reported by a third of this group with difficult to treat CCH patients is promising and could be clinically meaningful if confirmed in further prospective (and preferably controlled) studies. There are little data on placebo effect from controlled trials in (refractory) CCH patients. In one randomized controlled trial of non-invasive vagus nerve stimulation (nVNS), 40% (18/45) of CCH patients in the nVNS group experienced a more than 50% reduction in attack frequency during the last 2 weeks of the randomized period, which was significantly higher than the 8.3% (4/48) in the control group [21]. Comparison to our results should be done with caution, since the patient characteristics in this study could be significantly different from our population, as it included CCH patients regardless of medication history and no information was provided on previous standard of care prophylactic treatments.

No serious adverse events were reported in this series. The main theoretical safety issue is the close proximity of the intervention to the vertebral artery, a structure that is known to have some anatomical variation and is at risk of damage, especially at the C1 level [22].

The major afferent contribution of the occipital and suboccipital deep and cutaneous structures is thought to be mediated by the spinal root and nerve of C2 and the C1 nerve has generally been considered to have no significant sensory function [1, 2, 23]. In a cadaveric study, a C1 dorsal root was present in 60% (48 out of 80) of specimens. Only 30% (14 out of 48) of these dorsal roots were found to have a distinct dorsal root ganglion [24].

This suggests part of this treatment is directed at a structure that is absent in a big part of the population. Interestingly, the stimulation of C1 in patients with chronic occipital pain evoked periorbital and frontal pain in the subgroup of six migraine patients only, suggesting that C1 has a particular link with migraine; there were no cluster patients included in this study, but a similar phenomenon cannot be excluded [23].

Overall, the rationale for targeting C1 is less convincing. It seems to be theoretically more dangerous than the other cervical levels, and there is less experience than with targeting C2 which has also been studied in other indications [25]. A suggestion for further research is to consider targeting only C2 or to target C2 and C3 (as nociceptive input of C3 projects to the trigeminocervical complex too).

Since solid data from a prospective study are lacking, we can only speculate on the potential place of PRF treatment at the high cervical level in the interventional treatment algorithm of CCH. The way forward is a prospective controlled trial.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest regarding this work.

Ethical approval This study was approved by our institutional ethical review board and was in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments.

Informed consent For this retrospective study formal consent is not required.

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