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Pulsed Radiofrequency Neuromodulation in Interventional Pain Management—A Growing Technology

Brandon R. Cohen, DO *, Edward T. Soriano, DO

Sinai Hospital Baltimore, Baltimore, MD

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A B S T R A C T

The objective of this article is to review literature on the history, proposed mechanism, and clinically relevant information on pulsed radiofrequency neuromodulation (PRF). We collected a variety of publications reviewing the safety and efficacy of PRF for various conditions commonly encountered in the field of pain management. Numerous randomized control trials, prospective series, and case reports have been published studying PRF. Many of the publications used for this review were case reports and clinical trials evaluating the safety and efficacy of PRF. Although there is evidence in some studies of the efficacy of PRF, results are occasionally conflicting or inconclusive. PRF is a safe and effective modality with a rapidly growing body of evidence to support its use in a number of clinical conditions. These conditions include headaches, radicular pain, chronic shoulder pain, axial low back pain, knee and hip pain, and peripheral nerve pain. Further studies are needed to determine which clinical conditions respond best to this therapy.

Introduction

Pulsed radiofrequency neuromodulation (PRF) therapy has been advocated as a safe and effective procedure with the potential to help patients suffering from pain in multiple body parts whose supplying nerve or nerves can be reached with a radiofrequency probe under fluoroscopic or ultrasound guidance. The objective of this article is to explore the existing literature on the wide variety of uses of PRF in the modern clinical setting for painful conditions refractory to other more standard pain management or operative treatments.

History and mechanism of action

Radiofrequency signal generators for medical use have existed in some iteration or another since at least the 1950s (Bogduk, 2006). The first application in pain management came in 1974 when continuous radiofrequency (RF) was used to deliver thermal energy via a percutaneous probe with an electrode tip for the purpose of ablating a nerve (Bogduk, 2006). Since then, RF has been used to create heat lesions at or near nerves or ganglia to relieve pain transmitted from these targeted nerves, often at temperatures around 67°C for targets such as the dorsal root ganglion (DRG) and 80°C to 90°C for targets such as the nerves innervating the cervical, thoracic, and lumbar facet joints (Bogduk, 2006).

Interestingly, studies comparing RF and PRF of the cervical spinal DRG found no outcome differences on whether lesions were performed at 40°C or 67°C (Slappendel et al., 1997). It has been demonstrated that temperatures of 40°C are not damaging to tissues, whereas temperatures of 67°C are tissue destructive. Therefore, it was theorized that the neuromodulatory effect of creating a strong electrical field in the proximity of the target nerve rather than the thermal lesion itself may produce the beneficial effects of RF treatment. However, it should be emphasized that although the technical aspects of RF and PRF are similar, they should be considered as essentially different procedures with different indications (Vallejo et al., 2013), with RF producing neural ablation and PRF being a neruomodulatory therapy.

PRF was developed with the goal of delivering short pulses of electromagnetic signals to target nerves which allow heat to dissipate, thereby avoiding neuronal damage. The advantage to this approach is the theoretical absence of the risks associated with thermodestructive lesioning, including deafferentation pain, or thermal lesioning of undesired tissues (Hamann et al., 2006). The current recommended protocol for PRF is the delivery of a 50,000-Hz electromagnetic signal in 20-ms-long pulses at a frequency of 2 pulses/s. The almost half second in-between pulses has been shown

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* Corresponding author: Brandon R. Cohen, Sinai Hospital Baltimore, 2401 W Belvedere Avenue, Baltimore, MD 21215.
E-mail address: brandon.r.cohen@gmail.com (B.R. Cohen).

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to allow enough time for any generated heat to dissipate and prevent any thermal tissue destruction (Bogduk, 2006).

Because PRF does not reach neuroablative temperatures, it is proposed that its mechanism of action lies in the creation of a strong electric field near the electrode tip, reaching upward of 185,000 V/m. An electric field of this magnitude has been shown to induce changes at nerve synapses and change nerve permeability independently of the heat effects of continuous RF. Histologic samples of tissue after PRF exposure have also demonstrated abnormal mitochondria morphology and disruption of microfilaments and microtubules (Chua et al., 2011). An additional proposed mechanism of action is the alteration in c-Fos signaling pathways. Expression of c-Fos is an indirect marker of neuronal activity, and its presence in nerves indicates the presence of a strong electric field (Byrd & Mackey, 2008). It was recently shown by Hagiwara et al. that PRF may also enhance descending noradrenergic and serotonergic inhibitory pathways that are involved in the modulation of neuropathic pain (Hagiwara et al., 2009).

An additional possible mechanism of action was very recently investigated by Hailong et al., 2018. The authors compared PRF to sham PRF in 96 rats that had undergone sciatic nerve ligation or sham sciatic nerve ligation. The sciatic nerve ligation served as an experimental model for chronic constriction injury in the rats. For clinical markers, the authors used the 50% paw withdrawal threshold and the thermal withdrawal latency, which are objective measures of responses to noxious stimuli. For biochemical markers, the authors measured glial cell line–derived neurotropic factor (GDNF) that was hypothesized to be an additional factor involved in physiologic response to PRF. The authors observed a statistically significant drop in the 50% paw withdrawal scale in the group that got PRF treatment compared with that in the sham PRF group at 6 days ($p < .05$) and even more so at 14 days ($p < .01$) after treatment (Hailong et al., 2018). A similar drop in thermal withdrawal latency was observed at 2 days after procedure ($p < .05$) and even more so from day 6 until day 14 ($p < .01$) (Hailong et al., 2018). The biochemical marker being investigated, GDNF, was found to be expressed higher at the ligation site in the PRF group at day 6 and 14 than in the same group before treatment and also than the levels in the sham PRF group at all time points ($p < .01$) (Hailong et al., 2018). This observed correlation between GDNF upgregulation in nerve tissue after PRF and symptomologic improvement in rats seems to suggest that GDNF upregulation may also play a role in the observed analgesic effects of PRF in humans.

Clinical uses of PRF

Headaches

The anatomy of the greater occipital nerve renders it susceptible to compression by cervical skeletal musculature. Irritation of the occipital nerve from compression or direct trauma may result in occipital neuralgia (ON) and cervicogenic headaches (Austad, 2004). In addition, it has been postulated that migraine headaches may also result from compression of neural structures in the cervical and occipital region (Zhang et al., 2011).

The greater occipital nerve arises as the medial branch of the dorsal ramus of the C2 spinal nerve, courses through the semispinalis muscle, and then traverses fascial planes to innervate the occiput medially (Austad, 2004; Zhang et al., 2011). It has also been observed that botulinum toxin chemoblockade of the semispinalsis muscle can provide months of relief from migraine headaches (Austad, 2004). This serves as the theoretical basis for the argument that the etiology of some migraine headaches may be peripherally mediated.

Cohen et al. published a randomized, double-blinded study comparing PRF with corticosteroid injections to the greater occipital nerve in patients with suspected cervicogenic headache (Cohen et al., 2015). Eighty-one patients received a bupivacaine plus lidocaine block and then either 32-minute cycles of PRF or 0.75 mL of 40-mg/mL methylprednisolone acetate (Depo-Medrol). The PRF group experienced greater pain relief than the steroid group at all follow-ups, but the apparent benefit decreased over time, most notably falling off between 6 weeks and 3 months when measuring worst occipital pain on the visual analog scale (VAS) (Cohen et al., 2015). The subgroup of patients with migraine headaches experienced a significant drop in average occipital pain between baseline and 6 weeks ($p < .001$) as well as 6 months ($p = .036$). Migraineurs also experienced a significant drop in worst occipital pain at 2 weeks and 3 months ($p = .024$). The authors did not observe any statistically significant reduction in severe headache frequency or in nonpain secondary measures such as headache-related disability, sleep quality, medication reduction, or depression score.

ON is a paroxysmal, shooting or stabbing pain in the posterior scalp in the distribution of the greater, lesser, or third occipital nerve, sometimes accompanied by numbness or dysesthesia in the distribution of the affected nerve (Choi & Jeon, 2016). Conventional treatment for ON includes nerve blocks to the affected nerves using local anesthetics and corticosteroids. Recent literature suggests that this often provides transient benefit that some patients and providers may find inadequate (Cohen et al., 2015). A published case series showed that in patients with ON, PRF application to the occipital nerves demonstrated longer pain relief (4–6 months) than corticosteroid injection alone (2–3 months) (VanderHoek et al., 2013). In addition, it has also been demonstrated that PRF combined with occipital nerve block with anesthetic and steroid showed significantly longer duration of pain relief than nerve block with corticosteroid and anesthetic alone (Gabrhelik et al., 2011).

The C2 DRG

The C2 DRG also may play a role in cervicogenic headache. As noted previously, the occipital nerve is derived from the C2 nerve root, and therefore, any compression of C2 may produce pain in the occipital nerve distribution. The C2 DRG occupies a large amount of space between the spinous processes of C1 and C2 vertebrae (Lu & Ebraheim, 1998) as shown in Figure 1 (Choi & Kim, 1998). This anatomy has been demonstrated by Bogduk to render the C2 DRG particularly susceptible to compression which is likely responsible for cervicogenic occipital headaches (Choi & Kim, 1998; Bogduk, 1999). Osteoarthritis of the C1-2 joint has also been shown to create pressure on the C2 nerve root causing suboccipital headaches (Lu & Ebraheim, 1998). Several publications have described the successful treatment of radiating occipital headache with the

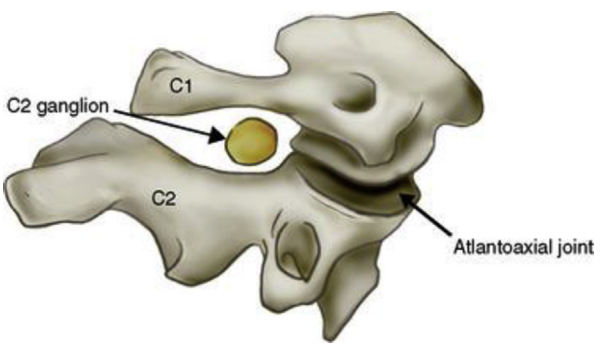

Figure 1. C2 nerve root ganglion. Choi & Kim, 1998