REVIEW ARTICLE

Dorsal Root Ganglion Pulsed Radiofrequency Treatment for Chronic Radicular Pain: A Narrative Mini Review

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Abstract:

Chronic cervical and lumbar radicular pain represents a very widespread neuropathic pain in the population with serious repercussions on the individual and social health.
To date, we do not have sufficient evidence available to allow us to make recommendations on the optimal therapy, despite the fact that various ways of treating root pain have been described over the years. Currently, conservative treatment of radicular pain relies on combined therapeutic, pharmacological and physiotherapeutic management.
Interventional therapeutic procedures are reserved for those patients with root pain refractory to conservative therapies.
Radio frequency (RF) can provide a good treatment option with Pulsed Radio frequency (PRF) modality.
We evaluate clinical and radiologic effects of the therapeutic outcome of pulsed radiofrequency (PRF) treatment adjacent to the dorsal root ganglion (DRG) for patients with chronic intractable lumbar and cervical radicular pain in this narrative minireview, describing mechanism of action, biological effects and evidence for clinical effects and safety in recently published studies.

Keywords: Chronic radicular pain; pulsed radiofrequency treatment; dorsal root ganglia; pain relief.

Introduction:

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain that arises as a direct consequence of an injury or disease affecting the somatosensory system." It represents one of the most difficult pain syndromes to treat. Conventional treatments often give unsatisfactory results [1-3].
Despite the efforts of the International Association for the Study of Pain (IASP), great confusion still remains due to divergent opinions among physicians on the definitions of neuropathic pain, somatic referred pain, root pain and radiculopathy [4].
One type of neuropathic pain is radicular pain, described as pain that occurs in the back and radiates to the limbs and caused by irritation / inflammation of the nerve roots, mainly due to the escape of material from the nucleus pulposus and / or from compression.
[5].

Epidemiology of Radicular Pain:

Cervical radicular pain affects approximately 1 (0.1%) of 1000 adults [6] while lumbosacral radicular pain, described as low back pain with leg pain extending below the knee, occurs at an annual prevalence in the general population of 9.9% to 25%. The point prevalence (4.6%– 13.4%) and lifetime prevalence (1.2%– 43%) are also very high, [7] which means that lumbosacral radicular pain is presumably the most commonly occurring form of neuropathic pain [8-9]. The health burden in the therapeutic management of lumbosacral radicular pain is very high, not only compared to all other forms of neuropathic pain, but also for many other chronic diseases, such as diabetes, heart failure and cancer [10]. Lumbosacral radicular pain resolves completely or partially in 60% of patients within 12 weeks of onset [11]. However, a large percentage of patients (20% to 30% of patients) have continuous pain 3 months to 1 year after onset [12].

Treatment of radicular pain with Pulsed Radiofrequency (PRF):

To date, we do not have sufficient evidence available to allow us to make recommendations on the optimal therapy, despite the fact that various ways of treating root pain have been described over the years. Currently, conservative treatment of radicular pain relies on combined therapeutic, pharmacological and physiotherapeutic management [13-19]. Interventional therapeutic procedures are reserved for those patients with root pain refractory to conservative therapies. Evidence suggests that lumbar epidural corticosteroid injections offer short-term relief from radicular pain and disability after acute herniated disc [13]. Vascular complications, however, are not uncommon, and the therapeutic efficacy of long-term epidural injections in terms of resolution and relief of lumbosacral radicular pain is however discussed. Radio frequency (RF) can provide a good treatment option. The efficacy of RF adjacent cervical DRG treatment for the management of chronic cervical root pain has been demonstrated in two small randomized controlled trials (RCTs) [20-21]. These studies show that RF is superior to sham surgery and RF at 67 ° C produces pain relief similar to RF at 40 ° C. However, a well-designed RCT comparing RF adjacent to lumbar DRG with sham surgery did not demonstrate significant pain relief for the management of lumbosacral radicular pain [22]. This lack of radiofrequency efficacy for lumbosacral root pain and the combined potential risk of deafferentation pain at electrode tip temperatures above 42 ° C [23] has prompted an ongoing search for safer and more efficient

techniques in clinical practice in recent years. A pulsed radiofrequency treatment was therefore developed for the therapeutic management of chronic pain, including radicular pain [24]. The idea of pulsed radiofrequency (PRF) was born after a completely chance meeting in 1993 and the first PRF procedure, conducted on a lumbar dorsal root ganglion, took place on February 1st 1996 [25-27]. Since then there has been a succession of various reports of using pulsed radiofrequency successfully for the treatment of a myriad of pain conditions, including cervical root pain, facial pain including trigeminal neuralgia (TN), joint pain sacroiliac, facet arthropathy, shoulder pain, postsurgical pain, radicular pain, groin pain and myofascial pain conditions [28]. The rationale behind the development of PRF was essentially to expand the treatment possibilities that serve the interest of the patient [27]. In general, there are two types of PRF procedures. The first category is formed by those procedures, where continuous radiofrequency (RF) has provided us with a satisfactory method, such as thermocoagulation of the medial branch. In this category, the potential contribution of PRF would probably be modest at best and although PRF is just as effective as thermal or conventional RF in this category, the adoption of PRF allows us a significant reduction in complications or side effects. The second type of procedure is where continuous RF has limited indications. This includes PRF treatment for peripheral neuropathies, arthrogenic pain, painful trigger points, and PRF application of the dorsal root ganglion in patients with neuropathy or radiculopathy [29].

Mechanism of action

The mechanism of action of PRF is not well known and is now the subject of increasingly in-depth research. At the moment, most of the scientific research carried out explains that its action consists in a neuromodulatory type synaptic alteration [30-31]. However, there is an ongoing discussion about whether the PRF effect is even ablative, albeit minimal. However, considering the physical events around the electrode, even if some level of destruction occurs during PRF, the degree of clinical relevance is questionable. The PRF, in fact, has shown a considerable safety margin.

Physics

During PRF treatment various biological changes can occur in the tissues due to thermal effects, high intensity electric fields, or as a result of both. PRF applies short pulses of RF signals with heat production determined by power deposition. Commercially available RF generators provide PRF signals with pulse durations ranging from 5 to 50 ms and pulse frequency ranging from 1 to 10 Hz, but the most commonly used sequence is a pulse frequency of 2 Hz and a pulse width of 20 ms [23]. The intrinsic RF oscillation frequency within each pulse is still about 420 kHz, the same as RF. In PRF, the pulse width is only a small percentage of the time between pulses, so the average rise in tissue temperature for the same RF voltage is much less for PRF than for RF. For this reason, it is possible to apply higher voltages to the PRF electrode than those commonly used in RF, without causing an increase in the mean temperature of the tissue near the electrode in the denaturation range greater than 45 ° C. PRF was initially thought to have no elevated thermal effects, but in vitro experiments have demonstrated the occurrence of brief elevations of temperature “heat spikes” around the needle

tip to about 45°C–50°C, depending on the tissue impedance [25]. If the pulse width is decreased, furthermore, for example from 20 ms to 10ms, the magnitude of these peaks can also be reduced [25]. We do not know if these transient "heat spikes" can have an ablative effect. In general, PRF can produce much stronger electric fields than RF. However, since the electric fields decrease rapidly with increasing distance from the tip, the resulting destruction is minimal. Just 0.5 mm away from the tip, the strength of the electric field drops exponentially to only a fraction of its initial magnitude [25]. Majority of the target tissues are thus subjected to low or moderate-strength electric fields, which may, in fact, play an important role in the mode of action of PRF. Electric fields can have plausibly significant effects on cells because of the transmembrane potentials that they induce. The induced transmembrane potentials can result in tissue disruption that could, in fact, be even more specific than that caused by heat. These effects occur at subcellular and biomolecular levels without substantially elevated temperatures. Ion channels disruption, resting, and threshold potentials alterations are all possible effects. The transmembrane potential generated is proportional to the electric field strength. The high transmembrane potentials can cause electroporation which is the process of deformation, pores creation, and if high enough, the rupture of the cell membranes [25, 32]. The phenomena induced by lower electric fields, which represent the main explanation of the effects of PRF, can theoretically cause long-term depression (LTD), as possible sequelae of the stimulation of conditioning [25, 27]. In that view, the low frequency of pulses and the high voltages in PRF induces LTD of synaptic transmission at the spinal cord, and in so doing, antagonizes the long-term potentiation that is purported to underlie many chronic pain states [27, 28]. This, however, does not explain the observed effects of PRF when used in areas of the body where there is no nerve tissue near the electrode tip, such as intra-articular PRF [29, 33].

Biological effects:

In a study evaluating the histological effects of continuous RF at 67 ° C and those of PRF applied adjacent and contiguous to the dorsal ganglia of rabbit spinal nerve roots, Erdine et al. [34] found mitochondrial degeneration and a loss of nuclear membrane integrity in the group where continuous RF was used but not in the PRF group. In another histopathological study, where the effects of continuous RF and PRF delivered at 42 ° C on rat DRG and sciatic nerve were compared, however, no structural changes were found, apart from transient endoneurial edema and the deposition of collagen between the two RF techniques [35]. More recent studies conducted on axonal ultrastructural changes have shown microscopic damage after exposure to PRF, such as alterations in the membranes and morphology of mitochondria, rupture and disorganization of microfilaments and microtubules [36]. We highlight two extremely informative in vivo studies. In a first in vivo study, conducted by Tun K et al., the application of PRF to the hind leg of rats, after tight ligation of the spinal nerves L5 and L6, induced a significant reduction in mechanical allodynia [37]. In another study, Aksu et al. [38] evaluated the effects of PRF after tight ligation of the sciatic nerve in rabbits. Mechanical and thermal hyperalgesia returned to baseline after 4 weeks in those animals that underwent PRF, unlike the groups that did not receive this type of treatment. All of these findings suggest that PRF treatment adjacent to the dorsal root can actually induce relief of neuropathic pain. In addition, greater

expression of c-Fos (an early immediate gene used as a marker for neuronal activity) was found in the dorsal horn of the spinal cord 3 hours after PRF treatment adjacent to the DRG, but not after RF [39]. This difference in c-Fos expression after treatment with PRF adjacent to the DRG compared to treatment with RF then disappeared after 7 days [40]. These results suggest that the effects of the early phase on neuronal activation in the spinal cord differ between RF and PRF, but not in the late phase. It should be noted that c-Fos is a limited marker of neuronal activity and does not differentiate the possible effects of RF and / or PRF on afferent pain signaling. Application of PRF adjacent to the DRG resulted in an up-regulation of activating transcription factor 3, a marker of cellular stress, in both small and medium caliber neurons of the DRG [41]. The application of PRF adjacent to the DRG, therefore, correlates with a short- and long-term increase in neuronal markers in the DRG and dorsal horn. Electron microscopic studies have shown only small histological changes after use of PRF adjacent to the DRG, such as enlargement of the endoplasmic reticulum cisterns or increase of cytoplasmic vacuoles. Conversely, RF at 67 ° C resulted in significant changes, such as mitochondrial degeneration and loss of nuclear membrane integrity [34, 42]. A different effect on myelinated nerve fibers was also observed depending on the RF or PRF application on the sciatic nerve. The radiofrequency resulted in severe WD of the distal peripheral nerve, while the PRF only changes in myelin configuration [37]. However, small electron microscopic changes were also observed after PRF was applied to the sciatic nerve. They mainly concern unmyelinated C fibers and thinly myelinated A-δ fibers [36]. This preferential effect of PRF on nociceptive C- and A-fibers could explain the differential analgesic effects without significantly interfering and thus affecting tactile sensory input. In summary, PRF is less neuro destructive than RF, primarily affects nociceptive axons C and A-and induces short- and long-term changes in neuronal markers in the dorsal horn and DRG.

Available evidence of efficacy of the treatment in the management of cervical and lumbar radicular pain:

Lumbar radicular pain:

In recent years, various scientific studies have been published evaluating the effects of PRF in chronic neuropathic lumbar radicular pain. There is however a great clinical heterogeneity among all these studies, due to different clinical evaluation parameters used and other interventions before or immediately after the PRF procedure, such as transforaminal epidural steroid injections (TFESI) or local anesthetics. Since all these parameters affect interpretation of the results is very difficult to perform adequate meta-analysis with higher level evidence. Chang et al. [43] found relief from radicular pain as measured by the Numerical Rating Scale (NRS) compared to pre-treatment baseline status in both the bipolar and monopolar PRF therapy groups. However, the reduction in NRS scores was significantly greater in the bipolar PRF group. Lee et al. [44] compared the use of transforaminal epidural steroid injections (TFESI) in combination with PRF treatment with PRF treatment alone in participants with lumbar root pain and cervical root pain. Although pain intensity (by VAS) was significantly lower in both groups after treatment, there was no statistically significant difference between groups for all time points [44]. Two RCTs, Koh et al. [45] and Shanthanna et al. (2014) [46], included two groups of participants, one receiving active PRF treatment

and the other sham treatment. However, there were differences in inclusion criteria and post-PRF procedures between those studies [45- 46]. Koh et al. [45] included participants six weeks after TFESI. No statistically significant difference was observed at three-month follow-up in mean NRS values between groups. However, when NRS scores were adjusted to 0 at baseline, the decrement from baseline was larger in the PRF group compared with the sham treatment group [45]. An RCT performed by Shanthanna et al. [46] showed a greater decrease in VAS scores in the PRF group at all follow-up time points but the differences between groups were statistically insignificant [46]. The study by Sluijter et al. [24] was a retrospective cohort study comparing the efficacy of continuous radiofrequency with PRF. They used the perceived global effect (GPE) as a measure of treatment success. The continuous RF group was terminated after the inclusion of 23 participants due to unsatisfactory results. At the six-week follow-up, 20 participants in the PRF group and only one in the continuous RF group had a GPE greater than 75%, which was defined as treatment success [24]. There were eight before and after comparisons studies [47-54]. They included a total of 383 participants, which in general showed significant pain relief after PRF treatment alone or in combination with nerve blocks and TFESIs. In a our recent experience with a single-center prospective longitudinal study a significant clinical radiological correlation of the benefits of PRF treatment was demonstrated [55]. In fact, a significant reduction in the VAS score after treatment was found compared to the pre-treatment baseline assessment, associated with a significant volume reduction of the respective DRG where the PRF was applied [55]. An in vivo biological effect was therefore demonstrated in this clinical study [55].

Cervical radicular pain:

The RCT about PRF for cervical radicular pain, by Van Zundert et al. (2007) [56], included 23 participants comparing active PRF treatment (N:11) and sham treatment (N:12); patients were followed up at one, three, and six months. Participants received segmental diagnostic blocks in order to confirm the affected DRG level; those who showed at least a 50% reduction in VAS pain were scheduled for PRF treatment. At three months, nine of 11 participants in the PRF group and four of 12 from the sham group achieved at least a 50% reduction in GPE. A reduction of pain intensity of 20 VAS points was achieved in nine of 11 participants from the PRF group and three of 12 from the sham group [56]. Three before and after comparisons included 58 participants in total who were followed up to one year, and the majority of participants showed at least 50% pain relief during that period. Before PRF treatment, participants received diagnostic DRG blocks or TFESIs [57-59].

Safety of the treatment:

Most of the studies conducted in PRF-treated patients with lumbar and radicular pain are safe, as described by Vuka I. et al. [60]. Four studies reported minor Adverse Events (AEs) related to pain during needle insertion [45], aggravated root pain [44], headache and increased back pain [46] and postoperative discomfort [24]. Five studies reported no adverse events at all [48, 52, 58, 61]. Only one study from the PRF treated cervical radicular pain group reported did not show AEs [62].

Reflections on the costs of treatment:

The average cost of a PRF treatment is about 800-900 euros, depending on the used PRF devices, but we think it is acceptable considering the individual and social costs.
With this treatment the patient can benefit from a recovery of optimal quality of life and above all he can interrupt therapies with analgesic and anti-inflammatory drugs for a fairly long period

of time (even 9-12 months) and return to daily work activities, contributing to the increase of overall social productivity of society, both in economic and civil terms. To give an example, even in developing countries the cost of common low back pain and lumbar radiculopathy represents a significant social problem. In Black Africa in the study of Fianyo et al. [63] financial cost of common low back pain and lumbar radiculopathy amount to 107.2 $ US (extremes: 5.8 and 726.1 $ US), while non-financial cost were: disruption in daily activities (94%), impact in emotional and sexual life (59%), impact on the family's budget (69%), abandon of family's projects (58%) or of leisure (42%) [63]. In black Africa top priority is given to the fight against infectious diseases those cause an important mortality. But common low back pain and lumbar radiculopathy, those have social and economic impact, should be given more attention [63].

Conclusions:

Treatment of neuropathic radicular pain with PRF applied to DRG is effective and safe as reported by most of the published studies. However, they generally have a non-randomized design with multiple limitations and rely on a relatively small number of highly selected participants. Therefore, these results should be interpreted with caution and it is not possible to generalize these results to all patients with painful neuropathic conditions. These results should be confirmed in high quality RCTs with a sufficient number of homogeneous participants and uniform comparators

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