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Review Article

Pulsed Radiofrequency: Current Clinical and Biological Literature Available

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ABSTRACT

Objective. Pulsed radiofrequency, where short bursts of radiofrequency energy are applied to nervous tissue, has been used by pain practitioners as a non- or minimally neurodestructive technique, alternative to radiofrequency heat lesions. Clinical advantages and mechanisms of this treatment remain unclear. The objective of this study was to review current clinical and laboratory data.

Design. We systematically searched the MEDLINE database (PubMed) and tables of contents of electronically available pain journals. Reference lists of relevant reports and international scientific pain congress abstract books were also hand searched. Only those reports on pulsed radiofrequency were withheld.

Results. The final analysis yielded 58 reports on the clinical use of pulsed radiofrequency in different applications: 33 full publications and 25 abstracts. We also retrieved six basic science reports, five full publications, and one abstract.

Conclusions. The accumulation of these data shows that the use of pulsed radiofrequency generates an increasing interest of pain physicians for the management of a variety of pain syndromes. Although the mechanism of action has not been completely elucidated, laboratory reports suggest a genuine neurobiological phenomenon altering the pain signaling, which some have described as neuromodulatory. No side effects related to the pulsed radiofrequency technique were reported to date. Further research in the clinical and biological effects is justified.

Key Words. Radiofrequency; Pulsed Radiofrequency; Neuropathic Pain; Chronic Pain

Introduction

Radiofrequency (RF) heat treatments have been used for over 30 years for a variety of pain syndromes: cervicogenic headaches [1], occipital neuralgia [2], whiplash injury [3], cervical radicular pain [4–6], intercostal neuralgia [7], lumbar radicular pain [8,9], mechanical low back pain due to the zygapophyseal joints dysfunction [10–13], discogenic pain [14,15], and pain associated with the sacroiliac joint (SIJ) [16–18]. Systematic reviews of RF heat treatments show limited to moderate evidence of its utility [19,20]. Recently, Hooten et al. [21] have cautioned the use of systematic reviews to estimate the clinical utility of RF neurotomy for low back pain, due to methodological shortcomings they found in three randomized controlled trials (RCTs).

The rationale for the application of RF denervation is the assumption that selectively heating

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nervous structures can impede nociceptive input. Practically this is achieved by percutaneous placing small-size electrodes at target neural tissues, to produce size-controlled lesions. However, others have questioned the utility of thermal lesioning, which is essentially neurodestructive, in the presence of neuropathic pain, and have shown that application of continuous low-temperature RF is as effective as RF heat lesion [6].

In 1998, Sluijter et al. [22] applied high-voltage RF current in bursts of 20 ms per 500 ms, permitting the generated heat to be washed out during 480 ms "silent phase." This idea of applying high-voltage energy near a nerve without subsequent heat-induced nerve injury with pulsed radiofrequency (PRF) was appealing. Initial clinical investigations had shown that PRF could be used safely as an alternative to heat lesions in patients suffering from refractory pain [23–26]. However, today, it is still not clear what are the differences and/or advantages between PRF and RF, both in terms of clinical outcome and biological mechanisms involved.

Pulsed radiofrequency treatment is a new technique for which evidence is gradually growing. New treatments evolve slowly in clinical (pain) medicine [27], and it usually takes a 10-year delay to accumulate sufficient clinical evidence in order to confirm or refute the value of the new treatment and present it in standard texts and reviews [28]. In RF case, it took even 26 years for lumbar RF facet denervation to establish its utility, between the first report in 1975 [29] and the first systematic review published in 2001 [19]. Therefore, constructing evidence for a new technique according to Evidence Based Medicine (EBM) guidelines is evolutionary. It usually starts with case reports and retrospective analysis, and if these give encouraging results, prospective trials on larger number of patients are carried out. Finally, RCTs and systematic reviews are performed [30]. On the other hand, basic research must precede clinical trials to elucidate putative mechanisms of action. The objective of this review was to examine the current evolution of PRF and determine what evidence is still necessary to validate this therapy.

Methods

We systematically searched for studies reporting on PRF. We searched the MEDLINE database (PubMed), Science Citation Index, Cochrane database, and Current Contents without language restriction using the free text terms: pulsed radiofrequency, radio frequency, radiation, isothermal radiofrequency, and combination of these (Table 1). The electronically available tables of content of the recent issues of pain journals were also screened. Reference lists of relevant retrieved reports and international scientific pain congress abstract books were also hand searched. The information from abstracts that were published as a full article later on was not taken into account. We classified the information according to the type of study reported. We did not analyze reports dealing with RF (non-PRF) techniques. Date of last electronic search was August 2005.

Results

The search yielded 301 potentially relevant reports, 243 were subsequently excluded (Figure 1). Forty trials reported on PRF not in medical applications, 14 reports were eventually not about PRF procedures, 32 reports were on human or animal effects of mobile phone radiation Global System for Mobile, 33 reports were of procedures using PRF in cardiac interventions, and 62 described the use of PRF in radiological interventions (magnetic resonance or Doppler echography).

Sixty-two reports were on the biological effects of PRF (Figure 2). Excluded were 26 reports on cellular and DNA effects of high-frequency current from mobile phones and other sources, seven reports on effects on tissue (muscle, cartilage), three were on the auditory effects of PRF, two on fertilization, three on osteogenesis, three on animal behavior, three on diathermal effects, and nine nonclassified. Thus, for final analysis and critical reading, 58 clinical reports (33 full publications and 25 abstracts) and six laboratory reports (five full publications and one abstract) were describing the effects of PRF.

Table 1 Search strategy

Search terms
Search "pulsed" [All Fields] AND "radiofrequency" [All Fields]
Search "pulsed" [All Fields] AND "radio" [All Fields] AND "frequency" [All Fields]
Search "pulsed" [All Fields] AND "radio-frequency" [All Fields]
PRFN
Isothermal radiofrequency; isothermal radio frequency
Thermocoagulation radio-frequency radiation
And REFERENCE Lists of Articles

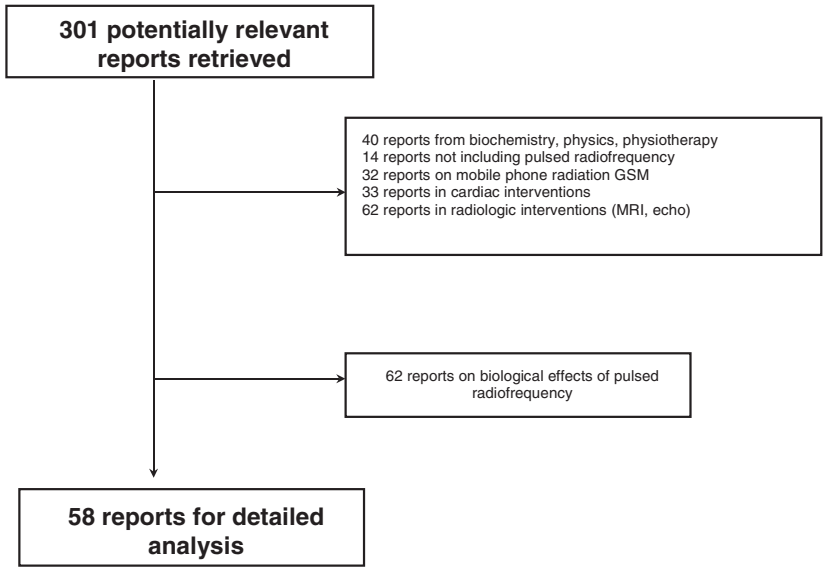

Figure 1 Flow chart of included and excluded trials and reports on pulsed radiofrequency.

A flow chart of the complete literature search is summarized in Figures 1 and 2.

Clinical Reports on Percutaneous Pulsed Radiofrequency

The clinical reports on percutaneous PRF are summarized in Table 2.

Prospective Trials

We found four prospective trials in 122 patients: one full publication and three abstracts presented at international scientific pain congresses. The pilot study on PRF in cervical pain syndromes showed that 13 of 18 patients with cervicogenic headache and cervicobrachialgia treated with PRF adjacent to the cervical dorsal root ganglion (DRG) for 2 min reported satisfactory pain relief of at least 50%, 8 weeks post-treatment. One year later, six patients continued to rate their treatment outcome as good or very good [26]. In another report, PRF was applied adjacent to the DRG for 8 min in 30 consecutive patients who suffered pain that could be anatomically ascribed to discrete dermatomes [31]. The authors suggest that PRF may be more effective in the management of neuropathic pain as opposed to

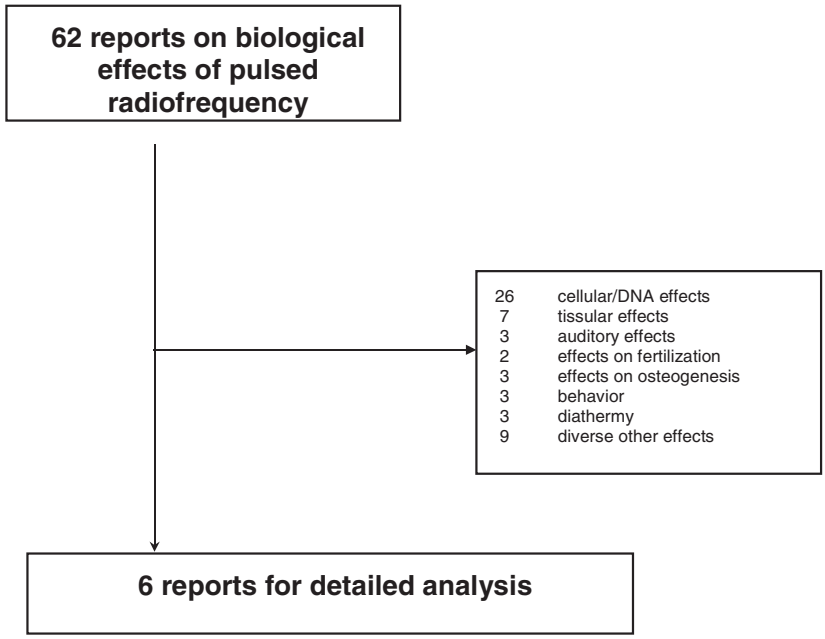

Figure 2 Flow chart of included and excluded trials in basic science. GSM = Global System for Mobile; MRI = magnetic resonance imaging.

Table 2 Clinical reports on percutaneous pulsed radiofrequency

Publication	Country	Indication(s)	Structure	Type of Study	Number of Patients	Outcome
Abejon et al. 2004 [38]	Spain	Lumbar radicular pain	DRG/lumbar	R	61	Subgroup analysis on FBSS, HD, and SS. Significant VAS reduction for HD and SS after 6 months, no effect in FBSS
Abejon et al. 2005 [48]	Spain	Glossopharyngeal neuralgia	Glossopharyngeal nerve	CR	2	5–7 points of pain reduction (VAS) for >6 months
Ahadian 2004 [44]	USA	Cervical (17) and lumbar facet pain (52), sacroiliac joint pain (39), cervical (39) and lumbar radicular pain (25), compound fracture (4), peripheral nerve lesion (25), CRPS (12), pelvic pain (12), cervicogenic headache (9)		R	194	% overall response (excellent and good) after 3 months: cervical (71) and lumbar facet pain (56), sacroiliac joint pain (66), cervical (40) and lumbar radicular pain (64), compound fracture (75), peripheral nerve lesion (52), CRPS (58), pelvic pain (50), cervicogenic headache (88)
Bayer et al. 2004 [42]	USA	Head and facial pain	Sphenopalatine ggl	R	46	At 4–52-month follow-up 20% of patients report complete pain relief and 65% mild to moderate pain relief
Bostyn et al. 2003 [61]	Belgium	Trigeminal neuralgia	Gasserian ggl	CR	13	Immediate pain relief in 92% of pts; postherpetic neuralgia 80% pain free at 3, 6, and 12 months. Atypical facial pain mean duration of pain relief 2.8 weeks
Castellanos 2004 [33]	USA	Shoulder pain	Suprascapular nerve	P	52	71% of the patients have pain reduction after 6 weeks (2.3 reduction on NRS)
Cohen and Foster 2003 [51]	USA	Groin pain and orchalgia	Ilioinguinal, iliohypogastric, genitofemoral nerves	CR	3	Complete pain relief at 6 months
Erdine 2001 [62]	Turkey	Trigeminal neuralgia refractory to other treatments, including conventional RF	Gasserian ggl	CR	5	2 patients only 2 weeks' pain relief and 3 patients no pain relief
Erdine 2004 [37]	Turkey	Failed back surgery syndrome	DRG/lumbar	R	15	After 6 months 60% of the patients report decrease in VAS (2.3-point reduction on VAS pain score), 66.6% an improvement in SF 36 physical function and 60% report a decrease in SF 36 bodily pain
Ferrer-Garcia and Nitu 2004 [53]	Spain	Sacroiliac joint (2) and low back pain (6)	?	CR	8	Significant decrease in VAS: 7/8 patients reduce analgesic use after a mean duration of follow-up of 5.4 months

Gauchi 2000 [54]	UK	Discogenic pain	L2 DRG	CR	39	48.8% improvement rate 6 weeks postintervention
Gofeld 2003 [55]	Israel	Meralgia paresthesia	Lateral femoral cutaneous nerve	CR	1	Pain free for 6 months
Hamann et al. 2002 [56]	UK	Neuropathic pain	DRG/lumbar	CR	1	Selective action of PRF on DRG cells after 2-month follow-up
Kamran 2004 [35]	Qatar	Cervicobrachial pain	Cervical medial branch	R	52	Significant decrease in VAS in 77% of the patients (VAS from 7.5 to 1.7) 6 months after treatment
Kane et al. 2002 [41]	UK	Shoulder pain secondary to cuff tear arthropathy	Suprascacular nerve	R	12	After an average follow-up of 4 months 9/12 patients show an improvement of the VAS (2-point reduction) and the Constant Shoulder Score, 10/12 show an improvement in sleep, no significant increase in shoulder range
Kuthuru et al. 2003 [57]	USA	Postherpetic neuralgia	Supra orbital and frontal nerves	CR	1	2-week effect with mixture of pharmacological treatment—follow-up n.a.
Mikeladze et al. 2003 [34]	USA	Chronic zygapophyseal joint pain (lumbar post FBSS and low back pain, and cervical pain)	Medial branch/lumbar and cervical	R	114	>50% pain reduction in 60% of patients for more than 6 weeks. Average duration of pain relief ±4 months
Munglani 1999 [24]	UK	Neuropathic pain	3 lumbar DRG and 1 thoracic spinal root	CR	4	Good pain relief between 2 and 7 months
Munglani and Stauffer 2003 [47]	UK	Neuropathic-type sciatica, neck pain and cervicogenic headache, Morton's neuroma, low back pain, rectal pain, abdominal pain	Cervical (6) and lumbar DRG (29), local neuroma (3) lumbar sympathetic chain (4)	R	42	% long-term (5 weeks to 9 months) response: cervical (66) and lumbar DRG (48), local neuroma (100), lumbar sympathetic chain (75)
Nagels et al. 2004 [63]	Belgium	Refractory atypical facial pain	Gasserian ggl	CR	5	No long-term results
Padfield 2003 [52]	UK	Occipital neuralgia	DRG (C2–C3) PRF during 8 minutes	CR	7	PRF 8 minutes, all patients pain relief, in one lasting for 7 months
Padfield 2003 [31]	UK	Mixed pain syndromes	Relevant DRG PRF during 8 minutes	P	30	Mixed result, better in neuropathic pain than in nociceptive pain
Rohof 2002 [43]	The Netherlands	Shoulder pain (retrospective study) (37) + case reports on: supra orbital nerve (3); neuroma (18), lateral epicondylitis (7), interdigital nerve (7)	Suprascapular nerve and relevant structures	R	72	Shoulder pain mean VAS reduction 4.5, and increased mobility with a mean duration of 26.8 months. Other cases no detailed results
Ruiz-Lopez et al. 2004 [40]	Spain	Radicular leg or arm pain	DRG/cervical and lumbar	R	25	Addition of contrast improves results

Table 2 Continued

Publication	Country	Indication(s)	Structure	Type of Study	Number of Patients	Outcome
Ruiz-Lopez et al. 2004 [45]	Spain	Painful scar (5) and neuromas (6), CRPS with residual pain in the knee (3), occipital neuralgia (1), chronic epicondilitis (1)	Peripheral nerves	R	16	After 3 months average decrease in VAS 5.4; 1 pt needed 3× a repeat procedure and 3 pts 2× after 3 months
Shah and Racz 2003 [49]	USA	Chronic post-tonsillectomy pain	Glossopharyngeal nerve	CR	1	Complete pain relief for 8.5 months
Shah and Racz 2004 [50]	USA	Post-traumatic headache	Sphenopalatine ggl	CR	1	>17 months pain relief (post-traumatic headache)
Shinozaki et al. 2004 [46]	Japan	Mixed pain syndromes	DRG and other (?) structures	R	19	6 FBSS, 7 PHN, 6 CRPS, 17/19 patients show effect for a mean follow-up of 21 weeks, VAS decrease with 50%
Sluijter et al. 1998 [22]	The Netherlands	Unilateral leg pain or leg and back pain	DRG/lumbar	R	20	Decrease in VAS and improved Global Perceived Effect after 6 months
Sluijter et al. 2003 [39]	Switzerland	Low back pain or sciatica	DRG/lumbar	R	79	Impedance corresponds inversely with result, temperature no role, no clinical outcome
Teixeira 2004 [36]	Portugal	Radicular low back pain due to hernia	DRG/lumbar	R	42	Mean follow-up 32.5 months, surgery avoided in 37 patients
Tekin et al. 2004 [58]	Turkey	Complicated whiplash	DRG/cervical	CR	1	90% pain relief for 5 months
Vallejo et al. 2004 [32]	USA	Sacroiliac joint dysfunction	Lateral branches L4–S3	P	22	73.9% good (>50%) pain reduction (VAS) or excellent (>80%); duration 6–32 weeks; and significantly increase quality of life scores
Van Boxem et al. 2002 [60]	Belgium	Idiopathic trigeminal neuralgia	Gasserian ggl	CR	5	9 procedures needed in 5 pts, clinical success for 5 months
Van Zundert et al. 2003 [26]	The Netherlands	Cervical radicular pain and cervicogenic headache	DRG/cervical	P	18	72% of patients ≥50% pain relief at 8 weeks. After 1 year 33% continue to rate treatment outcome as good or very good
Van Zundert et al. 2003 [25]	Belgium	Idiopathic trigeminal neuralgia	Gasserian ggl	CR	5	3/5 patients excellent effect for mean duration of 19.2 months
Yegul et al. 2004 [59]	Turkey	Shoulder pain	Suprascapular nerve	CR	3	Excellent pain relief during 1-week to 1-month follow-up

CR = case report/series; CRPS = comples regional pain syndrome; DRG = dorsal root ganglion; FBSS = failed back surgery syndrome; ggl = ganglion; HD = herniated disc; P = prospective study; PRF = pulsed radiofrequency; pt = patient; R = retrospective study; SF = short form; SS = spinal stenosis; VAS = visual analog scale; n.a. = not available; NRS = numeric rating scale.

nociceptive pain [31]. PRF treatment of the innervation of the SIJ (lateral branches L4–S3) was performed in 22 patients refractory to conventional treatment, including intra-articular SIJ injections with corticosteroids/local anesthetics. Seventy-three percent of the patients experienced good to excellent pain reduction, with significantly improved quality of life scores for a duration of 6–32 weeks [32]. In 52 patients with chronic shoulder pain, PRF treatment of the suprascapular nerve resulted in a decrease in pain in 71% of them after 6 weeks [33].

Retrospective Trials

We found 15 retrospective trials in 809 patients.

The use of PRF for the management of patients with zygapophyseal joint pain was documented in two retrospective studies, one on lumbar and cervical level [34] and the other on cervical level [35]. A total of 166 patients were treated, with a satisfactory clinical response of 3–6 months.

The first published trial on PRF reported on 20 patients following failed back surgery, treated with PRF adjacent to the lumbar DRG, resulting in a decrease in visual analog scale (VAS), less disability, and an improved global effect up to 1 year after treatment, without any postoperative discomfort [22]. Additionally, five retrospective trials on PRF treatment adjacent to the DRG, including 222 patients, were identified. Three of these studies evaluated clinical outcome with a good long-term response [36–38], and two other studies evaluated technical parameters, indicating the importance of impedance and the positive role of injecting contrast medium before PRF on clinical outcome [39,40].

One retrospective study on the management of shoulder pain secondary to rotator cuff tear arthropathy on 12 patients reported a reduction in VAS pain score of 2 points in 75% of the patients up to 4 months postprocedure [41].

One study on 46 patients with chronic head and facial pain who received PRF treatment of the sphenopalatine ganglion showed a mild to moderate relief in 65% of the patients for a duration of follow-up of 4–52 months [42].

Five retrospective trials reported on patients with different pain syndromes including: lumbar and cervical zygapophyseal joint pain, lumbar and cervical radicular pain, shoulder pain, SIJ pain, complex regional pain syndrome, pelvic pain, postherpetic neuralgia, peripheral neuralgia, neuromas, and others. In total, 343 patients were treated with satisfactory results [43–47].

Case Series and Reports

Finally, we found 18 case reports and case series including a total of 105 patients: two cases with glossopharyngeal neuralgia [48] and one case of chronic post-tonsillectomy pain [49], one post-traumatic headache [50], three patients with groin pain and orchialgia [51], four patients with chronic back pain syndromes [24], seven patients with occipital neuralgia [52], eight patients with SIJ pain [53], and 39 patients with discogenic pain responsive to L2 DRG block [54]. Other abstracts reported on cases with meralgia paresthesia [55], neuropathic pain [56], postherpetic neuralgia of head and face [57], complicated whiplash [58], and suprascapular nerve for shoulder pain [59]. In most of these case reports and retrospective trials, there was a good pain relief with follow-up periods varying between 30 days and several years. Five case reports related to PRF treatment of the gasserian ganglion of patients refractory to any other treatment and often with a general condition precluding more invasive treatment. Three [25,60,61] out of the five reports related positive outcome and two reports [62,63] no or little effect.

General Reviews

Sixteen reviews, editorials, letters, and comments discussing the use of PRF were found [30,64–77]. In general, most consider the use of PRF as a non- or minimally neurodestructive alternative to RF heat lesions, because its potential better risk/benefit balance, but there is also a call for higher-quality clinical research. This call is even more justified by the fact that in none of the clinical reports on PRF treatment neurological side effects or complications were mentioned.

Clinical Reports on the Transcutaneous Application

Randomized Clinical Trial

We found one double-blind randomized controlled study including 40 patients with temporomandibular joint (TMJ) arthralgia treated with PRF energy therapy [78]. The reduction of pain (numerical rating score) was significant for PRF and control groups ($P < 0.001$ and $P = 0.01$, respectively); however, only the experimental group showed a significant increase in mouth opening and lateral jaw movements. No side effects were reported during the treatment and the 2-week follow-up period. The authors concluded that PRF is a safe and effective treatment for TMJ arthralgia.

Prospective Trials

In addition, we found three prospective trials on transcutaneous neuromodulation therapy using

charge-balanced biphasic rectangular current, in phases of 200 ms with pulse repetition frequency varying from 4 to 10 Hz. One reported on radiating low back pain including 83 patients, with 59 completing the 3-month follow-up protocol [79]. There was a significant improvement in mean VAS scores, activity levels, and sleep over the whole observation period. The Oswestry Low Back Pain Disability scores improved as well.

Another case–control cross-over study reported twice, including 68 patients with nonradiating neck pain in which PRF stimulation was applied [80,81]. Reduced pain intensity, improved quality of sleep, and increased physical activity was observed, and no side effects were reported.

Case Report

One case report found that four patients, one patient with pain in the radial part of the wrist and the other three with failed back surgery syndrome (or postlaminectomy syndrome), benefited from short-term pain relief after transcutaneous PRF treatment [82].

Laboratory Reports

Six reports of laboratory experiments on the neurobiological effects of PRF on neural substrates, five full publications and one abstract, were available for critical analysis. PRF and RF current applied to the rat brain tissue both produced neuronal destruction 21 days after treatment; however, the ratio of neurodestruction was considerably lower in the PRF group (5.5%) compared with the RF group (14.6%) [83].

Exposure of the cervical DRG to PRF current showed a significant early increase in c-Fos immunoreactivity in the superficial laminae I and II of the dorsal horn, 3 h after the procedure [84], as well as 1 week after PRF and RF treatments [85]. It has recently been reported that the biological effect of PRF was unlikely to be related to an overt thermal damage and appears to be selective in that it targets the group of neurons whose axons are the small-diameter C and Aδ nociceptive fibers [86]. Finally, PRF was shown to have a differential effect compared with RF on excitatory postsynaptic transmission, as well as cell morphology, even when RF heat lesions are performed in normothermic conditions [87,88].

Discussion

After an extensive literature search, we could detect 42 reports from 11 countries on the clinical use of percutaneous and transcutaneous PRF in different applications on a variety of (chronic) pain syndromes in 1,207 patients. Up till now in none of the listed reports, neurological side effects or complications with PRF were mentioned. Because this is a new technique, a substantial part of these results are reported in the abstract books of international scientific pain congresses. Their number is increasing yearly, and they are progressively published in peer-reviewed journals. This is a similar evolution to other techniques in medicine in general, and pain medicine in particular. Although there is an increasing focus in the literature for PRF, the question still remains: "What is its place in the pain management algorithm?"

In order to answer this question, it is important to understand the concept behind RF and PRF treatments. It is presumed that the mode of action of RF heat lesions is that by selectively heating nervous structures, denervation can impede nociceptive input. However, the observation that after RF treatment pain relief lasts longer than the sensory loss in the relevant dermatome [22], gave rise to the theory that heat is not the only mode of action and that other factors responsible for pain relief may be involved. Furthermore, the role of heat was further questioned after the results of Slappendel et al. [6], who found no difference in patient outcome with RF treatment when an electrode tip temperature of 40°C was used compared with RF at 67°C. Thus, it was hypothesized that there must be another, perhaps additional, mechanism besides heat that alters pain signal transmission.

So PRF was conceived as a novel, potentially safer mode of administration of RF energy, whereby in 1 s, two bursts of 20 ms each of an alternating current are delivered. The oscillating frequency of the alternating current is 500,000 Hz. During one cycle, the "active phase" of 20 ms is followed by a "silent phase" of 480 ms to allow the generated heat to washout. The output is usually set at 45 V, but if the electrode tip temperature exceeds 42°C, the voltage is decreased.

In our review, we have shown that since the initial publication on PRF treatment for spinal pain in 1998 [22], information from prospective and retrospective trials, as well as several case reports on the percutaneous use of PRF, is accumulating, as illustrated in Table 2. Interestingly, the transcutaneous use of PRF, which is a different application, has been documented to provide good pain relief in different modes. The available infor-

mation on PRF treatment does not allow pooling the data because of the differences in the reporting, but also because of the fact that the technical parameters such as voltage, impedance, time of application of the PRF current, and resulting electrode tip temperature are not always reported. There is an urgent need for a more standardized data collection and reporting.

In general, RF stimulation within frequencies between 300 Hz and 300 GHz create electric fields, which generate both current and heat on exposed biological substrates. It is clear that heat lesions of neural substrates above 45°C result in nonselective destruction of both myelinated and nonmyelinated nerve fibers [89]. However, it has been shown that PRF and RF have differential neurobiological effects [87], aside from the heat-induced morphological changes; c-Fos activation, a marker for neuronal activity in the rat dorsal horn, has been reported to be expressed immediately (3 h) [84] and up to 7 days [85] after PRF treatment. The duration of Fos-like immunoreactivity exceeding the expected length of time for c-Fos expression caused by the acute effect of surgery and electrical stimulation of sensory nerves may be due to the inhibition of excitatory C-fiber responses as seen in long-term depression, according to an accompanying editorial [72]. Moreover, it has recently been reported that the biological effect of PRF was unlikely to be related to an overt thermal damage and appears to be selective in that it targets the group of neurons whose axons are the small-diameter C and Aδ nociceptive fibers [86].

We also found that PRF alters synaptic transmission. *In vitro* PRF stimuli of organotypic slices of the hippocampus induce transient decrease in excitatory postsynaptic potential with rapid and complete recovery, while in contrast, continuous RF creates long-lasting blockade of synaptic transmission even in temperatures <45°C. Both continuous and PRF treatments induce distance-dependent tissue destruction under the stimulating needle, but the effect was more pronounced in the continuous group [87]. Similarly, a morphological evaluation of the rabbit DRG 2 weeks after sham, continuous and PRF, illustrated no pathological findings in control and sham-operated group, minimal morphological changes in the PRF group, and neurodestruction in the continuous RF group [88]. All these findings together indicate that the effects of PRF are more reversible and less destructive than those of continuous RF, even when lesions are performed <45°C.

Despite the fact that PRF might operate by modulating pain perception rather than directly destroying neural tissue, at present it is difficult to relate the results of these experiences to clinical data. Little is known about how PRF procedures at frequencies and temperatures used in current clinical practice would modify central and peripheral components of pain pathways, and further well-designed *in vitro* and *in vivo* experiments are needed to clarify this issue. In addition, lesion parameters (sensory and motor stimulation thresholds), electrode position, lesion duration, and local tissue properties can all be important variables that may influence clinical outcome.

In face of this laboratory evidence, a recent editorial urged practitioners to conduct randomized clinical trials to demonstrate the effectiveness (or lack thereof) of PRF treatment and only then use these data as a tool to understand and advance the technique [72]. We find this statement troubling. Conducting sham-controlled RCTs in interventional pain management has been shown to have important methodological and ethical limitations [66,90–94]. Randomized clinical trials have indeed become the gold standard for assessing the effectiveness of therapeutic agents, but often produce inconsistent results [95] and can have limited external validity [96]. Furthermore, Concato et al. [97] and Concato and Horwitz [98] have recently reported that the results of well-designed observational studies do not systematically overestimate the magnitude of the effects when compared with randomized clinical trials.

Conclusions

Animal data suggest that PRF, as an alternative mode to administer RF energy, has genuine differential biological effects in cell morphology, synaptic transmission, and pain signaling, which are minimally destructive and nontemperature dependent.

The clinical data on the use of PRF are progressively accumulating, and up to now no neurological complications are documented. In order to further elucidate the mode of action of PRF and to define its true value in the management of chronic pain, more research on this promising technique is justified.

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