

Prospective Study

Effectiveness of Pulsed Radiofrequency with Multifunctional Epidural Electrode in Chronic Lumbosacral Radicular Pain with Neuropathic Features

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Background: Lumbosacral radicular pain is a common clinical finding with a statistical prevalence ranging from 9.9% to 25% in the general population.

Objective: To investigate the effectiveness of dorsal root ganglion pulsed radiofrequency (PRF) in patients with chronic lumbosacral radicular pain and neuropathic features.

Study Design: Prospective case series clinical outcome study.

Methods: We evaluated 34 patients with lumbosacral neuropathic pain who underwent PRF at the corresponding level of radicular symptoms distribution (ranging from L3 to S1). Each patient suffered a single leg-radiating pain with probable neuropathic features (assessed with clinical grading) lasting for > 6 months and unresponsive to previous treatments. A multifunctional PASHA-electrode® was introduced with trans-sacral access through a hollow needle, placed under fluoroscopic guidance into the lumbosacral epidural space and its active tip moved close to the dorsal root ganglion responsible of the clinical symptoms. After connecting the electrode to a generator, stimulation tests were performed and PRF was started and applied for 240 seconds at a frequency of 2Hz, amplitude of 45 V and a tip temperature between 40 – 42°C. If the pain involved more than a single nerve root, the electrode was placed at a different segment and the procedure repeated. Outcome measures included the pain intensity score on a 0 – 10 numeric rating scale (NRS) and the Italian Pain Questionnaire (QUID) at pre-treatment, one and 6 months post-treatment. *P* values < 0.05 were considered statistically significant.

Results: In comparison with pre-treatment, a significant reduction in pain score was observed in mean NRS either at one and 6 months (*P* < 0.001). The QUID - Pain Rating Index rank displayed a parallel trend at the first (*P* < 0.001) and last follow-up (*P* = 0.01). Moreover, a direct correlation between the 2 scales occurred, showing a parallel score decreasing (*P* < 0.001). Eighteen (52.9%) and 17 (50%) of 34 patients showed pain reduction in NRS > 2 points and > 30%, at one and 6 months, respectively.

Limitations: The non-controlled design of the study, the patients were heterogeneous, the small number of patients, and the duration of follow-up was limited to 6 months.

Conclusions: PRF of dorsal root ganglion performed with a multifunctional electrode for > 240 seconds appears to be safe and might be more effective than the classic 120 seconds needle-mediated approach. Therefore, it may be considered as a valuable tool for the treatment of lumbosacral radicular pain with neuropathic features.

Key words: PRF, radicular pain, neuropathic pain, DRG, NRS, PRIr-T, multifunctional electrode

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Lumbosacral radicular pain is a common clinical finding with a statistical prevalence ranging from 9.9% to 25% in the general population, whose main features are radiating leg pain in one or more lumbosacral dermatomes (with or without low back pain) and possible sensory or motor disturbances (1). It may be associated with several degenerative conditions of the spine such as herniated discs (2), although correlations between clinical and radiological signs may be minimal (3). Radicular pain can be nociceptive, neuropathic, or mixed, displaying metameric distribution and being commonly perceived either as deep or superficial by the patients. Prolonged orthostatism or sitting as well as significant physical efforts causing cumulative loading may be associated with exacerbation of symptoms while lying down usually leads to pain relief. Neurological examination, disclosing pain distribution, negative and/or positive symptoms, is the most important tool for sensory evaluation while some provoking maneuvers such as the straight leg raising or femoral stretch tests may confirm distribution of symptoms (4). Moreover, several clinical scales or questionnaires are available to help differentiate pain features and quantify neuropathic involvement (5). Modern surgical procedures are mostly focused on spinal decompression with significant short-lasting improvement but results are unremarkable over a long period (6). Therefore, it is commonly advised not to proceed with surgery unless severe or progressing motor deficits occur. Main conservative approaches to persistent spinal pain involve a first-line treatment with oral drugs (i.e., corticosteroids, nonsteroidal anti-inflammatory, or anticonvulsants) and physiokinetic therapy, whose main goal is pain control during the disease course. If ineffective, epidural or transforaminal injection of corticosteroids and, more recently, radiofrequency of the dorsal root ganglion (DRG) have become a second-line step (7).

Radiofrequencies are high-frequency electromagnetic waves delivered through a needle with exposed tip or with an electrocatheter (which allows the access to epidural space, placement of the active part of the electrode closer to the target, and local injection of medications), generating an electric field able to warm tissues up to 90°C and cause nerve focal damage (8). Continuous thermoablative radiofrequency has been progressively replaced by pulsed radiofrequency (PRF), thanks to its safer mechanism of action. PRF keeps the electrode tip temperature between 40°C and 42°C during the whole procedure, allowing dorsal root neuro-

modulation and preventing massive cell destruction. Therefore, PRF seems to cause microscopic and intracellular damage (e.g., mitochondria and cytoskeleton edema, disruption and disorganization of microfilaments and microtubules, myelin re-arrangement) subsequent to the application of an electric field on the DRG rather than to mild thermal effect (8-10). Several scientific works about PRF in radicular pain were performed with rigid needles while studies with flexible electrocatheters are not yet available. The aim of this study was to test the effectiveness of electrocatheter-mediated PRF in the treatment of radicular pain with neuropathic features.

METHODS

Study Design

The whole protocol was approved by the Institutional Review Board committee from the Santa Maria Maddalena Hospital. The patients were informed and allowed to withdraw from the study at any time if necessary. Before obtaining an informed consent, the procedure and associated potential complications, such as nerve root injuries or epidural space bleeding, were explained to the patients.

One hundred and fifty-six patients diagnosed with low back pain were consecutively evaluated between January 2011 and December 2013. Before undergoing PRF, all the patients enrolled had received standard treatments such as medications, physical therapy, and epidural injections, which had produced no significant change of pain intensity. Several patients underwent surgical treatment (mostly due to lumbar herniated or bulging disc) > 6 months before but not after being enrolled. Examinations and procedures have been done in the Pain Medicine Unit of Santa Maria Maddalena Hospital, Occhiobello (RO), Italy. All patients underwent a new clinical examination to assess if only radicular pain or if neuropathic involvement occurred (11-13). In order to evaluate neuropathic features (i.e., pain arising as a direct consequence of a lesion or disease affecting the somatosensory system) we relied on the Treed et al (14-17) grading system for neuropathic pain which has been confirmed as a useful tool for diagnosis, at times even more reliable than questionnaires.

We recruited adults over 18 years old with the following features:

1. Single leg-radiating pain (with or without low back pain) lasting for > 6 months;
2. Clinical examination suggestive of radicular pain

with > one positive provoking test (e.g., straight leg raising test);

3. Lack of significant improvement with pharmacological therapy, physical therapy, or epidural injection of anti-inflammatories;
4. Lack of significant motor deficits which cannot be subsequent to antalgic adaptation;
5. Magnetic resonance imaging (MRI) showing neural compression or spinal canal narrowing and/or electromyographic test suggestive of radiculopathy;
6. A definite or probable neuropathic involvement assessed with clinical examination and grading system.

We considered as exclusion criteria:

1. Low back pain more severe than a radicular component;
2. A possible or unlikely neuropathic pain;
3. MRI not compatible with clinical symptoms;
4. A positive response to previous treatments;
5. Patients affected by neurological or psychiatric disorders;
6. Radiculopathies with significant motor deficits requiring urgent surgery (e.g., cauda equina syndrome);
7. Reported allergy to anaesthetics.

The procedure was performed in a safe and quiet operating room which fulfilled the standards for disinfection and sterilization of devices with each patient lying on a fluoroscopy table in the prone position. After the injection of local anesthetic, a 15 G hollow needle was inserted with a paramedian access through the sacral hiatus. A small caliber (4 F) and flexible probe with 2 electrodes located at the tip (multifunctional PASHA-electrode®) was introduced through the needle, placed under fluoroscopic guidance into the lumbosacral epidural space and its active tip moved close to the DRG responsible of the clinical symptoms (which could range from L3 to S1). Proper placement of the catheter was confirmed with anteroposterior, oblique, and lateral fluoroscopic projections. After connecting the probe to a generator (PMG-230 Baylis Medical com. Inc. Canada), a 50 Hz sensory stimulation test with an output current below 0.6 V was applied to cause a tingling sensation in the area where the patient referred symptoms and confirm the correct catheter position. After, a 2 Hz motor stimulation with an output up to 2 V was also performed in order to ensure that no motor recruitment (except of local muscle twitches) occurred.

If impedance values were compatible with the proximity to the target (i.e., 200 – 400 Ohm), PRF was started and applied for 240 seconds at a frequency of 2 Hz (20 ms of current and 480 ms without stimulation resulting in 2 active phases/second), amplitude of 45 V, and a tip temperature between 40 – 42 °C (Fig. 1). If the pain affected more than a single nerve root, the electrode was placed at a different segment and the procedure repeated with the same technique. The probe was then removed and the patient was sent to the recovery room. The baseline features of the patients and procedure are shown in Table 1.

Outcome measures

Before undergoing PRF, each patient was evaluated with a bedside examination and pain questionnaires were administered. The intensity of pain was assessed with the 0 – 10 Numeric Rating Scale (NRS) and with the Italian Pain Questionnaire (QUID), a reconstructed Italian version of the McGill Pain Questionnaire consisting of 42 descriptors divided into 4 main pain rating index ranks (sensory, affective, evaluative, and mixed). The Total Pain Rating Index rank value (PRIr-T), given by the sum of all the rank values, describes and quantifies the pain (18-20). For each patient, pain was classified as “incident” if arising as a result of movement or “non-incident” if not associated with activity.

The follow-up was planned at one and 6 months and included clinical examination, NRS-, and QUID-based interviews. Response to treatment was considered successful with a pain reduction in NRS > 2 points and > 30% at one month. Clinical examination and data collection before treatment and during follow-up was done by 2 independent reviewers not involved with the PRF procedure.

Statistical analysis

A non-parametric Friedman test was applied to evaluate changes in NRS and QUID before and after the procedure. Post-hoc pairwise comparisons between baseline, one- and 6-month follow-up were done with the Wilcoxon’s rank sum test. The Spearman’s rank correlation test was performed in order to quantify the association between changes in the 2 pain scores, and to assess the influence of pain features (i.e., incident vs. non-incident) on NRS and QUID variations. The Kolmogorov-Smirnov test was used to assess gender differences in NRS before and after treatment. *P* values < 0.05 were considered statistically significant.

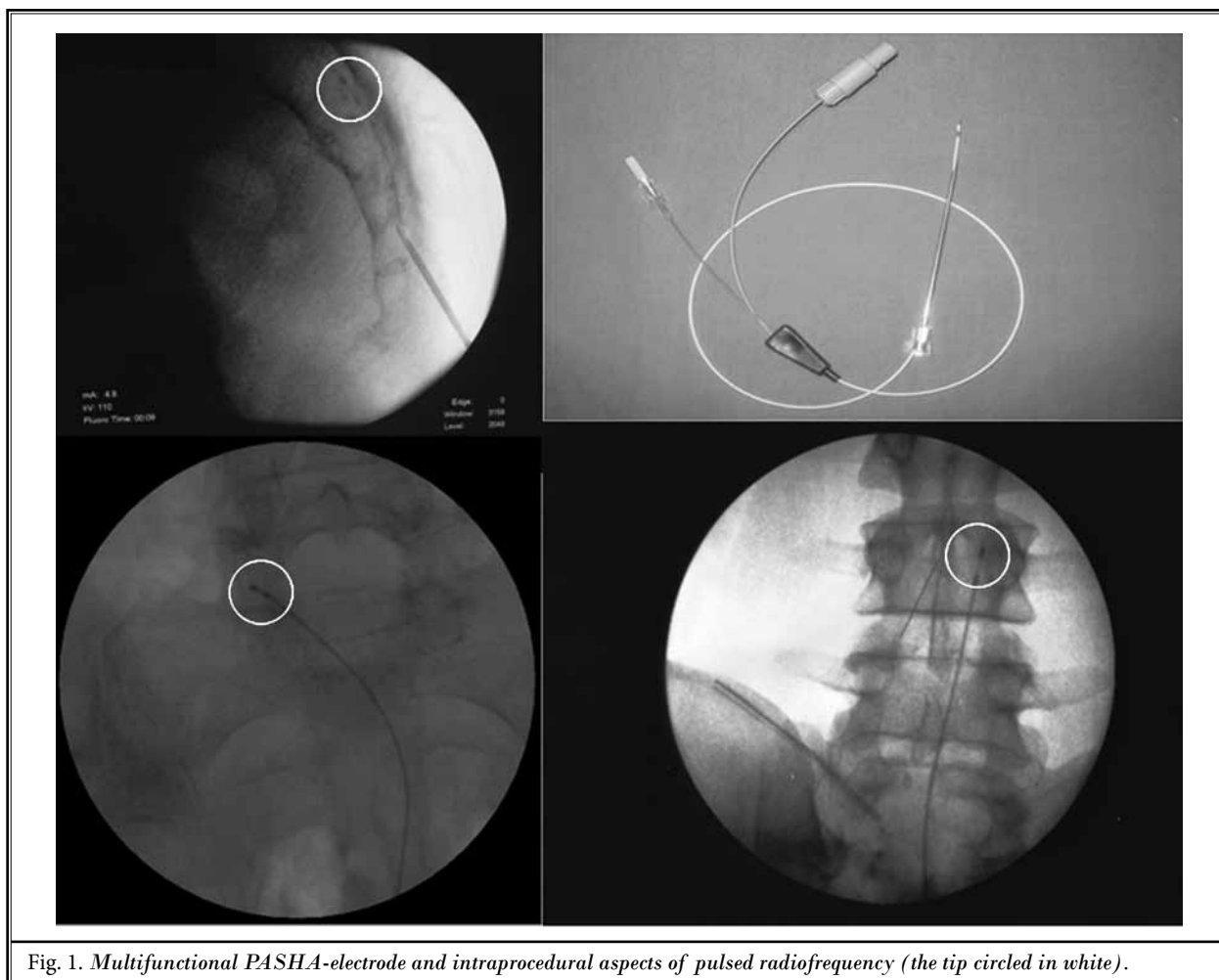


Fig. 1. Multifunctional PASHA-electrode and intraprocedural aspects of pulsed radiofrequency (the tip circled in white).

RESULTS

One hundred and thirteen patients were excluded from the study because they did not meet the selection criteria while 43 patients were enrolled. Nine patients were lost to follow-up at the first month as described in the study profile (Fig. 2). Although all of them returned within 6 months for the subsequent follow-up reporting no significant adverse effect related to the procedure, we chose not to include them in the study. The number of women in our population was higher than men ($P < 0.05$). No remarkable post-treatment adverse effects nor complications occurred. A summary of the PRF effect on pain scores is summarized in Table 2.

The Friedman test suggested significant changes in NRS ($\chi^2=30.15$, $P < 0.001$) following the PRF procedure. The post-hoc pairwise comparison with Wilcoxon test showed pain relief was maintained either at one- or

Table 1. Patient demographic and clinical characteristics.

n	34	
Age	64.1 (13.3)	
Males	10	
Females	24	
Levels treated	L3	4
	L4	9
	L5	15
	S1	13

Data are mean (SD) or n.

6-month follow-up ($P < 0.001$), if compared with pre-treatment. Moreover, statistical significance was not reached if the first follow-up was compared with the last one, suggesting that PRF analgesic effect did not fade with time (Fig. 3).

A significant variation in PRIr-T was also observed

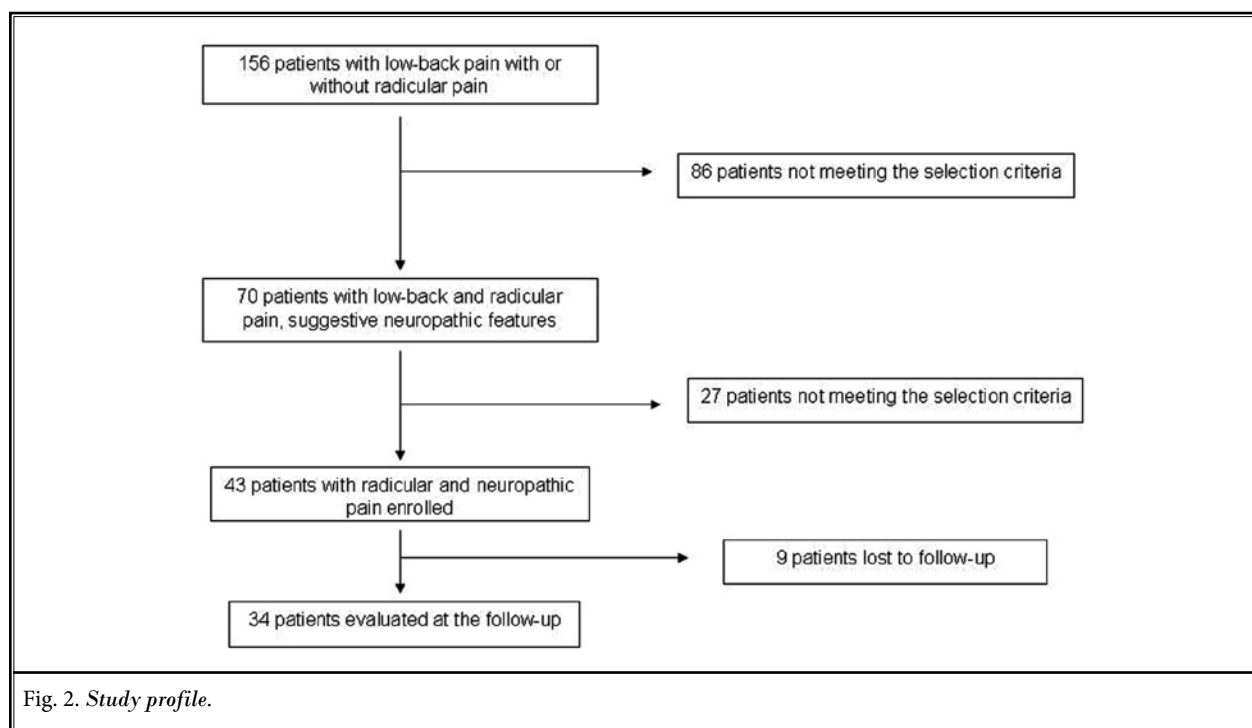


Fig. 2. Study profile.

Table 2. Change in pain scores following pulsed radiofrequency.

	Pre-treatment	1 ^o month	6 ^o month
PRIr-Total	24.53 (12.25)	19.21 (11.48)	18.85 (12.48)
PRIr-Somatic	0.31 (0.16)	0.25 (0.13)	0.26 (0.16)
PRIr-Affective	0.34 (0.19)	0.24 (0.19)	0.24 (0.21)
PRIr-Evaluative	0.31 (0.21)	0.23 (0.16)	0.21 (0.17)
PRIr-Mixed	0.28 (0.21)	0.18 (0.19)	0.19 (0.22)
Mean NRS	8.03 (2.14)	5.47 (2.83)	5.44 (3.16)

Data are mean (SD). PIRr = Pain Rating Index rank. NRS = Numeric Rating Scale.

($\chi^2=14.75$, $P < 0.001$) and the post-hoc analysis confirmed pain improvement after one ($P < 0.001$) and 6 months ($P = 0.01$). As observed with NRS, no significant difference occurred if the 2 follow-ups were compared (Fig. 4).

A direct correlation between pain improvement assessed with NRS and PIRr-T was found with Spearman correlation test after one ($\rho=0.69$, $P < 0.001$) and 6 ($\rho=0.65$, $P < 0.001$) months, strengthening the reliability of PRF effectiveness (Fig. 5). The same test failed to find a significant relationship between features (incident vs. non-incident) and reduction of pain after PRF.

A successful clinical outcome was observed in 18 (52.9%) and 17 (50%) of 34 patients, at 30 and 180 days, respectively. Moreover, the sample size allowed us to highlight a NRS reduction of 45% at one month and

43% at 6 months (> 99% of statistical power). Although the unequal gender distribution in our population, NRS improvement in both genders were not remarkably different at baseline nor at follow-up.

DISCUSSION

This study explored the effectiveness of flexible electrocatheter-mediated PRF lasting 240 seconds on lumbosacral radicular pain with neuropathic features. Our results highlighted half of patients reporting a significant pain reduction, confirmed with 2 validated different scores and mostly lasting for the whole follow-up period. Although a pain reduction > 50% is often reported in literature as a successful outcome, we considered reliable most of the scientific works suggesting > 30% of reduction as significant for clinical

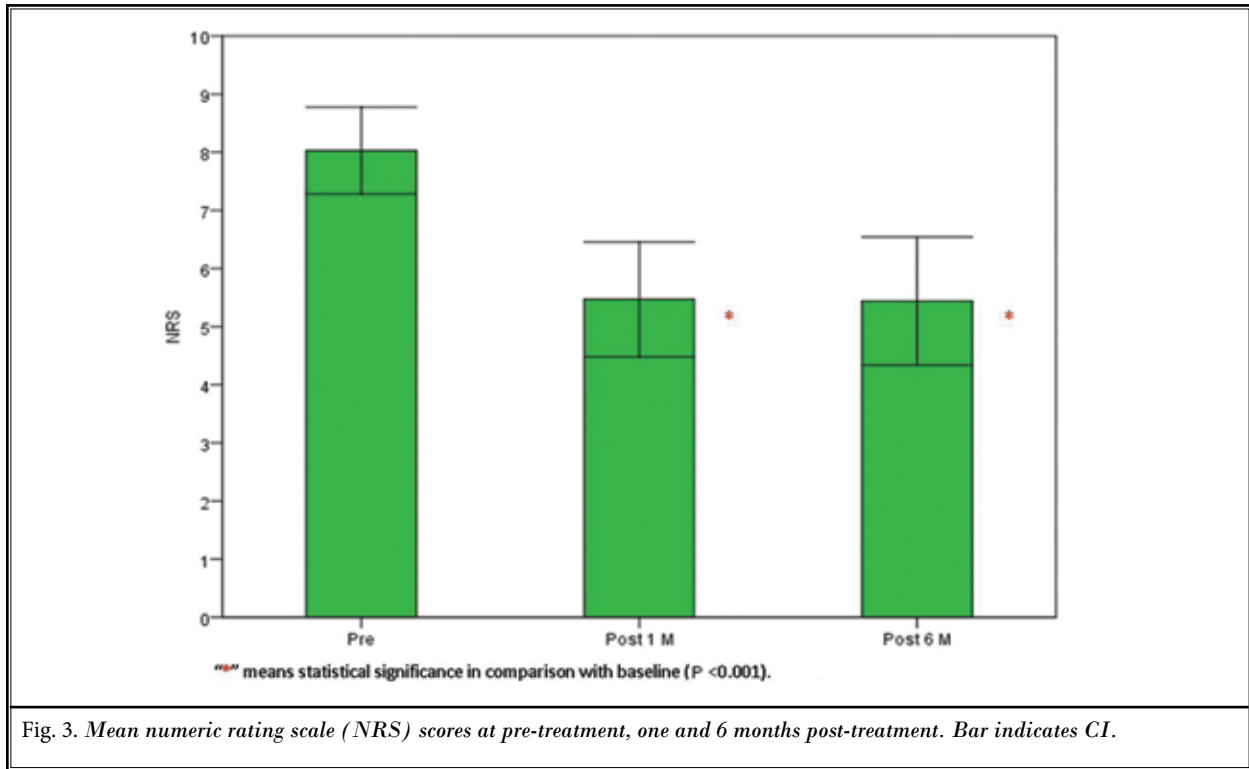


Fig. 3. Mean numeric rating scale (NRS) scores at pre-treatment, one and six months post-treatment. Bar indicates CI.

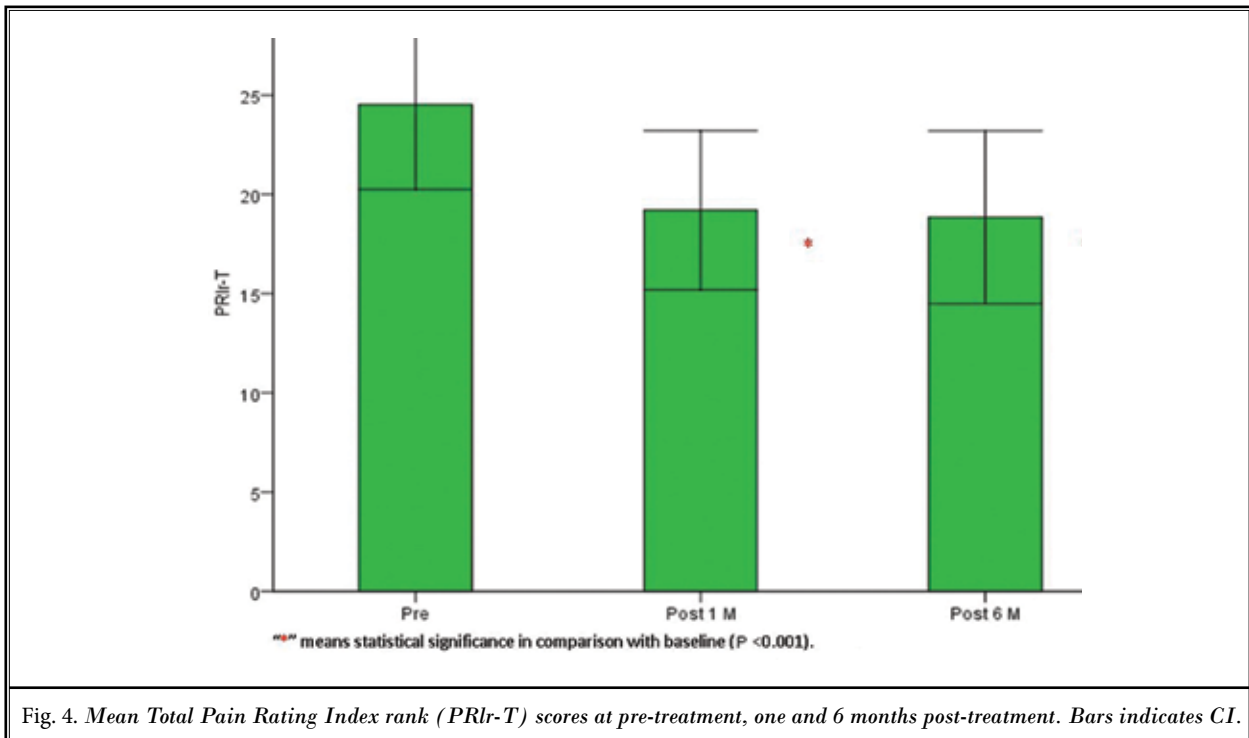
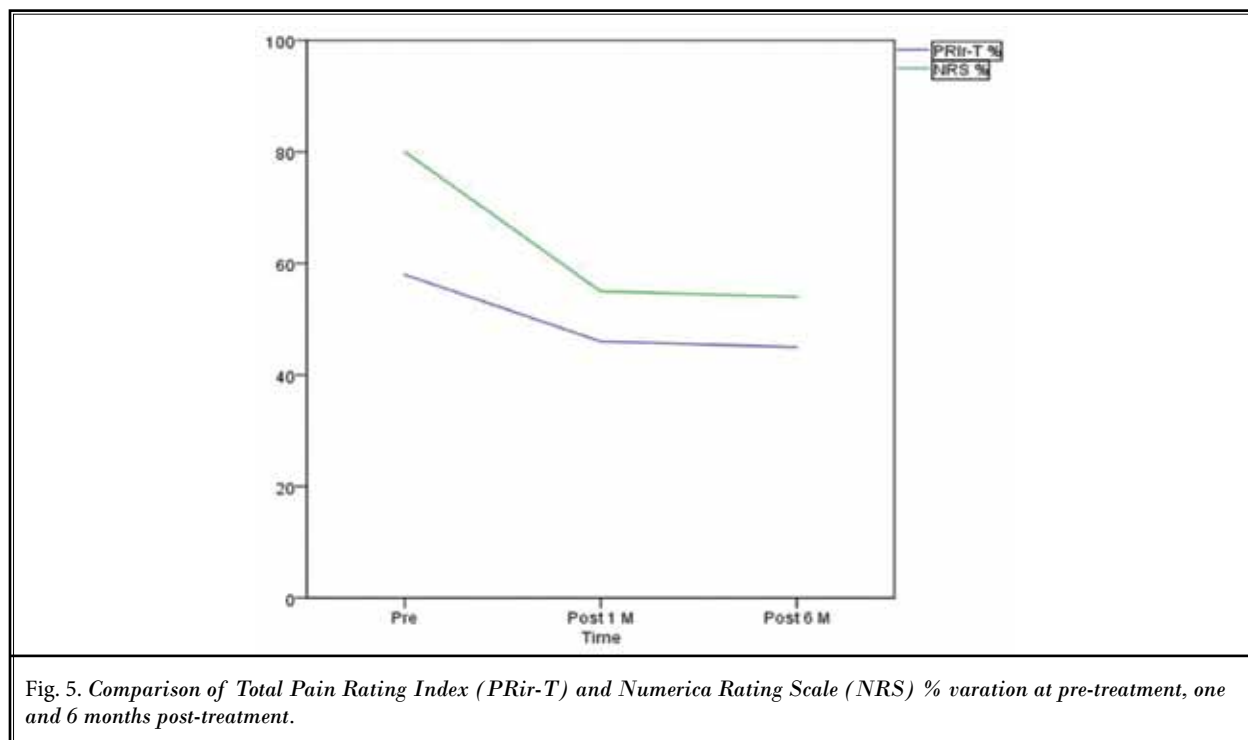


Fig. 4. Mean Total Pain Rating Index rank (PRlr-T) scores at pre-treatment, one and six months post-treatment. Bars indicates CI.



trials, especially if neuropathic features are taken into account (18,21-23).

The exact PRF mechanism of action and its therapeutic effects are still a matter of debate. It is assumed that the electric field generated by stimulation may promote microstructural changes in neural tissues which, in turn, would block pain transmission (24). Direct excitation of the DRG has been found to reduce neuronal excitability which may exert an analgesic effect by suppressing action potentials generation and propagation (10). Several authors suggest PRF could affect the transcription of different "pain genes" in the dorsal horn and nerve roots (e.g., increasing the expression of c-Fos and activating transcription factor 3/ATF3 or decreasing the calcitonin gene-related peptide/ CGRP), and act selectively on small-diameter A δ and C fibers inhibition (25,26). Microscopic studies displayed an increased level of ultrastructural damage such as swollen mitochondria in small-diameter neurons exposed to radiofrequency fields, with the highest degree of changes observed in C fibers if compared with A δ s and A β s (27). Moreover, radiofrequency of the DRG showed an immunomodulating effect, causing a shift in the immune system balance with a decreased production of pro-inflammatory cytokines such as TNF- α and IL-1 and a raised anti-inflammatory status (28). PRF

applied in recent pain models showed the activation of descending anti-nociceptive adrenergic and serotonergic pathways as well as a significant modulation of microglial expression (29,30). The development of neuromodulation due to plastic synaptic changes resembling the long-term depression have also been taken into account but, although intriguing, this hypothesis still remains speculative (31,32).

Unfortunately, few randomized controlled studies about PRF are available with non-univocal results and variable effectiveness in chronic lumbar pain (33). This may be a consequence of the heterogeneous spectrum of disorders responsible of lumbosacral pain and the lack of international consensus on the PRF procedure. For instance, most of studies featured a 120 second treatment, although its duration might be prolonged up to 480 seconds. Given the time of stimulation has been assumed to be a factor in neuromodulation and synaptic plasticity, it might represent an important issue to consider also in PRF along the voltage intensity, as suggested by previous studies (24,34). Therefore, we considered 240 seconds a more proper stimulation period.

Moreover, all the studies evaluated the effects of PRF performed with a needle and a transforaminal approach. In our opinion, the use of a multifunctional flexible electrode has several advantages in comparison

with rigid equipment, such as a closer stimulation (i.e., higher electric field density) of the DRG and the chance to infuse medications into the epidural space (33). Due to its geometric and structural features the probe can focus the electric field on the side rather than in front of the tip, which should allow significant neuromodulation with lower tissue heating and injury (35).

Considering the possible influence of gender as a risk factor for radicular pain development, an interesting issue to be considered in our study is the female:male ratio discrepancy (36). The patients included were affected by moderate-to-severe long-lasting pain with neuropathic features. It is commonly acknowledged a significant female prevalence for chronic, complicated radicular and neuropathic pain which, in our opinion, could give account for the gender discrepancy (37-39).

Last, although scientific evidence supports the PRF treatment mostly for radicular pain, no selection criteria dealing with the pain pathogenesis (i.e., nociceptive or neuropathic predominance) are usually considered. This might result in a statistical bias responsible of contrasting results about PRF effectiveness in scientific literature. Continuous radiofrequency is contraindicated in neuropathic pain but PRF has shown promising results (40). Recent experimental models of lumbosacral neuropathic pain have shown significant effects of radiofrequency in reduction of tactile and mechanical allodynia, suggesting it as an important therapeutic tool (41,42). Therefore, we considered it important to evaluate the treatment only in patients with probable neuropathic pain features. The significant relief of symptoms reported by our patients acquires even greater significance because neuropathic pain treatment still remains challenging for most of physicians (43).

A recent work published by Shanthanna et al (44) was the first randomized controlled trial testing the effectiveness of PRF treatment for chronic lumbar radicular pain. Their results highlighted a small effect of the treatment at 4 weeks and at 3 months, not significantly different from the patients in the placebo group. Nevertheless, the treatment was once again performed with a needle rather than a flexible probe, and the duration of treatment was only 120 seconds. In our opinion, these features may have affected the results, minimizing the potential effectiveness of PRF.

Therefore, it appears mandatory to develop guidelines shared by pain physicians and experts in order to exploit the full potential of PRF. The procedure effec-

tiveness in lumbosacral pain syndromes might be likely affected by several factors which should be taken into account for the next randomized controlled studies, such as the use of multifunctional electrodes, proper treatment duration, and stimulation intensity.

Limitations

The main limitation of the study lies in the non-controlled design and in the small and heterogeneous population enrolled. Nevertheless, in our opinion, the statistical power was strong enough to make our results reliable. Most of the patients with radicular pain are usually suffering from different diseases and a larger selection of patients would make enrollment too challenging. Moreover, other studies with large case series have not shown different responses to treatment between subgroups of patients with different pain pathogenesis (45). Although the change of pain medications as well as physical therapy during the follow-up was not considered in our study, the lack of response to treatments prior to enrollment was in our opinion enough to make PRF effectiveness reliable (28).

The percentage of patients lost to follow-up was significant. Nevertheless, in our opinion, the non-controlled design of the study (i.e., no risk of affecting the balance in groups receiving different treatments), the homogeneous clinical features due to the inclusion criteria, and the lack of treatment-related issues responsible for the first loss to follow-up, support the reliability of our results (46,47).

Considering the significant effects, another limitation is the follow-up duration of 6 months whereas PRF effects have been claimed to last up to 12 months in some studies (8,33). Therefore, we have no data on PRF's longer-term effects, which could be interesting to investigate in future studies.

CONCLUSIONS

Although preliminary, this study is the first to highlight the significant effects of PRF on chronic lumbosacral radicular pain with neuropathic features. Considering the challenge of treating neuropathic pain, these results should encourage pain experts to investigate the procedure, being aware of important issues such as the choice of devices or the stimulation parameters. Further randomized placebo-controlled studies with longer follow-up periods are needed to finally clarify PRF's effectiveness and its role as a tool against pain.

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