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Tapentadol prolonged release in association with analgesic radiofrequency for the treatment of chronic lumbar radicular pain: an observational, prospective study

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Abstract. – OBJECTIVE: Chronic pain is frequently irreversible, representing a major health problem. A survey has shown that 19% of European adults experience chronic pain which is not adequately managed. Innovative interventional techniques for the treatment of chronic pain have been developed, as a further step beyond the three-layer WHO analgesic ladder. Among these techniques, continuous and pulsed radiofrequency (RF) are very effective in the management of radicular pain syndrome. Usually, these techniques are associated with a pharmacologic approach with a wide-spectrum analgesic. Tapentadol has a double mechanism of action, as a μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibitor (NRI), contributing synergistically to its analgesic efficacy on both nociceptive and neuropathic pain.

PATIENTS AND METHODS: We aimed to test the efficacy of tapentadol prolonged release (PR) combined with pulsed RF in improving neuropathic symptoms and disability in 50 patients with moderate-to-severe chronic pain due to lumbar radiculopathy.

RESULTS: The responders to treatment, showing at least a 30% reduction in pain intensity on the Numerical Rating Scale (NRS), were 38 (76%). Both average NRS at rest and during loading were statistically significantly reduced compared with baseline (p<0.0001). Other parameters investigated (sleep quality, neuropathic symptoms, the degree of disability) were all statistically better with tapentadol PR. Patients requiring RF intervention dropped dramatically from 98% at baseline to 10% at the end of the study (p<0.01). Adverse events were reported in 14 patients (28%), four of which required therapy discontinuation. However, patients' satisfaction and overall tolerability of tapentadol PR treatment were high.

CONCLUSIONS: Tapentadol PR is effective in reducing pain intensity at rest and during loading, with a favorable safety and tolerability profile. Moreover, the use of tapentadol PR decreases the degree and severity of disability, as well as the intensity of neuropathic symptoms.

Key Words:
Tapentadol, Radiofrequency, Combined analgesia and radiofrequency.

Introduction

Acute pain related to a physical trauma is a naturally reversible symptom, whereas chronic pain is generally caused by conditions that are usually difficult to treat, with a consequent structural plasticity of the involved structures, becoming irreversible, and carrying both a physical and an emotional disability[1-6]. Pain therapy consists of a therapeutic and scientific approach to the treatment of pain, and it has considerably progressed in recent years. In Italy, pain medicine gained more and more interest over the years, probably due to the high number of people suffering from chronic pain. Some EFIC data[7-10] show that Italy is third in Europe for prevalence of chronic pain (26%) after Poland (27%) with a European average of 19%.

A wide-range treatment approach, including both analgesic drugs and interventional techniques, is one of the most innovative methods for rapid and effective management of chronic pain[11,12]. Among the most innovative techniques for the treatment of chronic pain, continuous radiofrequency (RF) over 43°C, and pulsed RF, with temperatures lower than 43°C, are very effective in the management of radicular pain syndrome, one of the most frequent causes of chronic neuro-

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pathic pain. Quite often, a disc-radicular conflict due to disc protrusion or lumbar or cervical disc herniation causes pain. In cases of a predominantly radicular pain without surgical indication, a valid alternative treatment is the stimulation of the radicular ganglion and of the nucleus pulposus of the intervertebral disc with RF. This procedure blocks the transmission of pain through various mechanisms and exerts an anti-inflammatory and immuno-stimulatory effect on the nervous tissue itself and on the whole organism. In approximately 60% of patients, the benefits of this treatment occur rapidly and persist for approximately 4 weeks and beyond. Conversely, the pharmacological management of chronic radicular pain, usually consists of analgesics with a wide spectrum of efficacy (both on the nociceptive component and on the neuropathic component of pain), which should guarantee an excellent tolerability even if administered for long periods.

Tapentadol, the forefather of a new class of analgesic drugs, has been recognized by the Italian Medicines Agency (AIFA) for its innovative value, and indicated for the treatment of severe chronic pain. In fact, tapentadol has an original and innovative double mechanism of action: as a μ-opioid receptor agonist (MOR) and noradrenaline reuptake inhibitor (NRI); both MOR and NRI contribute in a complementary and synergistic way to its broad-spectrum analgesic efficacy on nociceptive and neuropathic pain. The effectiveness of tapentadol prolonged release (PR) is equal or superior to that of strong opioids, while sharing with them only a part of the mechanism of action, approximately 40% of the μ-load, which confers to this molecule a peculiar tolerability profile: fewer opioid-induced effects connected to the μ-sparing effect[13-18]. All these aspects result in a significantly lower risk of treatment discontinuation, as well as in improved quality of life for patients. Furthermore, tapentadol PR shows a low risk of drug interactions. For all these characteristics, tapentadol PR is a favorable option for the treatment of chronic radicular pain. However, few data are available at present regarding the combination of tapentadol PR and RF treatments. Thus, the aim of this study was to test the efficacy of tapentadol PR combined with pulsed RF in improving neuropathic symptoms and disability in patients with moderate-to-severe chronic pain due to lumbar radiculopathy, and to assess patients' satisfaction for the combined treatment received.

Patients and Methods

Adult patients of either genders, between 18 and 75 years of age, with chronic radiculopathy and pain lasting at least 6 months, graded more than 5 on the Numeric Rating Scale (NRS), and eligible to the RF procedure without previous RF surgery within 6 months, were included in this observational, prospective study. The presence of major systemic illnesses, and previous RF interventions within 6 months from study enrollment, constituted the most important exclusion criteria. Patients were followed-up for at least 90 days. The study lasted 10 months, from March 2017 to January 2018. The local Ethical Committee approved the study design.

In opioid-naïve patients, treatment with tapentadol PR was started at a dose of 50 mg twice daily and up-titrated, if necessary, to a maximum dose of 500 mg per day. In patients already treated with strong opioids, the initial dosage of tapentadol PR was calculated according to the equivalent previous opioid's dosage. Concomitant analgesics were not allowed during the study period.

At the beginning of the study period, the initial visit T0 corresponded to the start of the treatment and to the first pulsed RF intervention. RF was performed with Neurotherm (Abbot Italia, Rome, Italy). Percutaneous intradiscal pulsed RF procedure of the intervertebral disc correlated to the radicular pain was performed with a fluoroscopic extradural oblique approach, placing the tip of needle in the center of nucleus pulposus and fixing temperature of lesion at 42°C for 20 min. Afterwards, during the retraction of the needle from the nucleous pulposus, it was placed in the corresponding intervertebral foramen near the dorsal root ganglion, where an infraneural stimulation at 42°C was performed for 6 min (Figure 1).

Subsequent follow-up was carried out either by telephone or during regular ambulatory visits, 30 days after enrollment (T30; telephone), 45 days after enrollment (T45; visit), 60 days after enrollment (T60; telephone), and after 90 days from enrollment (T90; final visit). After 45 days of treatment with tapentadol PR (T45), the responders to tapentadol continued the pharmaceutical therapy only, whereas non-responders underwent a new RF procedure followed by tapentadol therapy for 30 days.

Pain was measured according to a 11-point NRS. The primary endpoint of the study was the rate of responders to the combination of tapentadol PR + RF therapy. The responders were defined as patients with at least a 30% improvement

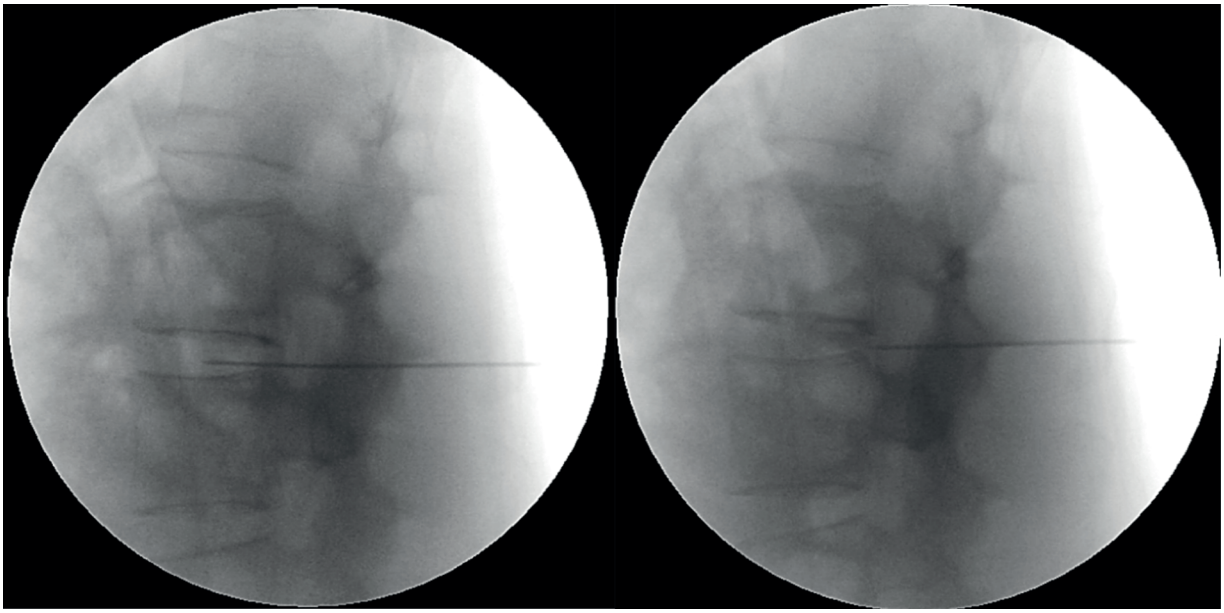

Figure 1. Intradiscal and infraneural approach to the dorsal root ganglion.

in the NRS for pain during loading, compared with the baseline value, after 30 days from the first RF procedure.

The secondary endpoints were: reduction in pain intensity at rest by 50% compared with baseline after 30 days of treatment, on the NRS; the quality of sleep assessed on a subjective verbal scale (0 = very disturbed, 1 = with frequent awakenings, 2 = good, 3 = restful sleep); the score reported on the DN4 questionnaire compared with baseline; any change in the disability index assessed through the Oswestry questionnaire. Moreover, the tolerability was assessed in all patients by recording all side effects that emerged during the study, with their severity.

Statistical Analysis

Statistical analysis was performed with Statistical Analysis System (SAS) 9.4 statistical software (SAS Institute, Cary, NC, USA). Data were analyzed by descriptive statistics; statistical comparisons were performed by the Student's t-test, the ANOVA test or the χ^2-test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

Patient population consisted of 50 subjects (22 males, mean age: 60.4 years, age range: 31–89 years). A total of 46 subjects (92%) completed the study with all scheduled analyses and follow-up visits. Radicular pain was caused by herniation (28 patients, 56%), disc protrusion (12 patients, 24%), lumbar stenosis (one patient, 2%), and a combination of disc herniation and protrusion (nine patients, 18%). Pain was mainly radicular (26 patients, 52%) or combined lumbar and radicular (24 patients, 48%), and it had been lasting approximately between 6 and 12 months in 11 patients (22%), between 12 and 24 months in 15 patients (30%), and more than 24 months in 23 patients (46%). Pain was either continuous (20 patients) or intermittent (30 patients), and in most cases (44 patients, 88%) neuropathic symptoms were present. Comorbidities are listed in Table I. Previous analgesic therapy consisted of a combination of paracetamol (52%), nonsteroidal anti-inflammatory drugs (NSAIDs) (86%), COXIB

Table I. Main existing comorbidities according to presence/absence of specific treatment.

	Total	
Comorbidities	**no.**	**%**
Respiratory	3	6.0
Endocrinology	15	30.0
Neurologic	3	6.0
Liver	2	4.0
Renal	2	4.0
Cardiovascular	25	50.0

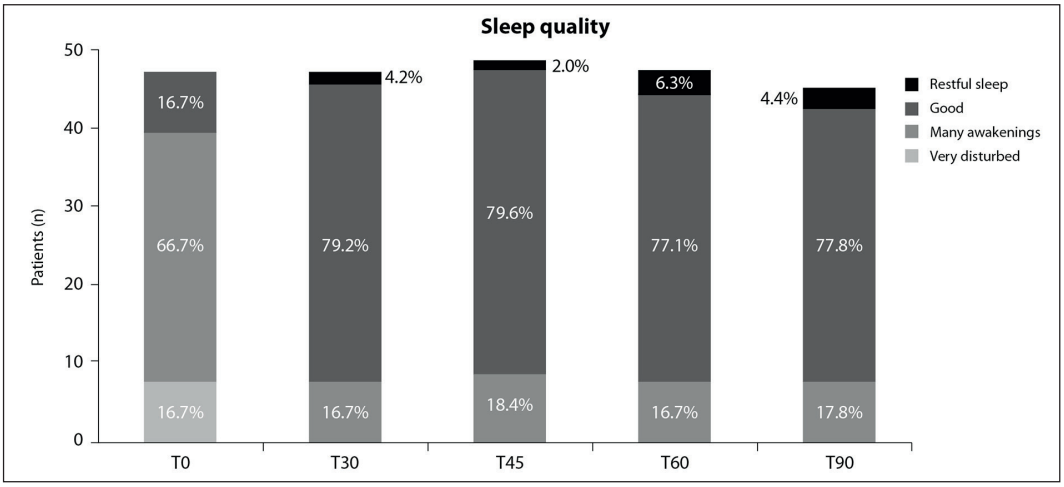

Figure 2. Sleep quality throughout the study.

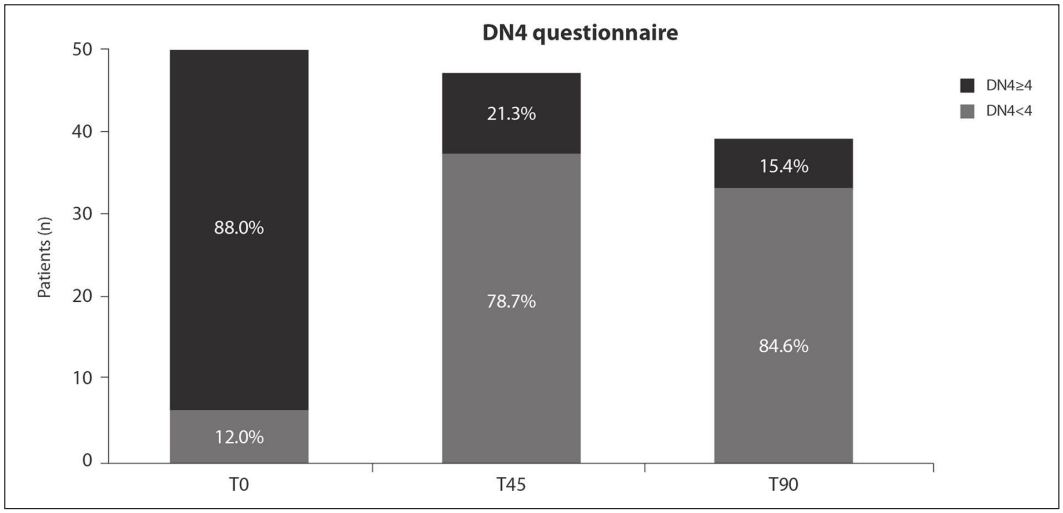

Figure 3. Neuropathic symptoms assessed during the study.

Table II. Pain intensity at rest and during loading over the study period, with mean and standard deviation.

NRS score	T0	T30	T45	T60	T90
Rest	8.2±0.88	5.0*±1.2	4.7*±1.5	4.5*±1.3	4.3*±1.39
Loading	9.0±0.66	5.1*±1.29	4.9*±1.48	4.6*±1.38	4.4*±1.26

*p<0.0001 *vs.* T0

(48%), and opioids (34%) with a reported poor efficacy (98% of patients) and poor overall tolerability (50%).

The average dose of tapentadol PR at T0 was 100 mg/day, increasing to a maximum dose of 200 mg/day at the end of the study. Tapentadol PR was graded as very effective in controlling pain intensity in 90% of patients, with an overall satisfaction for the treatment received reaching 98% at T30 and persisting at later follow-ups. At T30, there were 38 responders (76%). When considering a 50% reduction in pain intensity, only 14 patients were responders (28%). Average NRS at rest and during loading for each visit are reported in Table II. Both types of pain are statistically significantly reduced compared with baseline (p<0.0001).

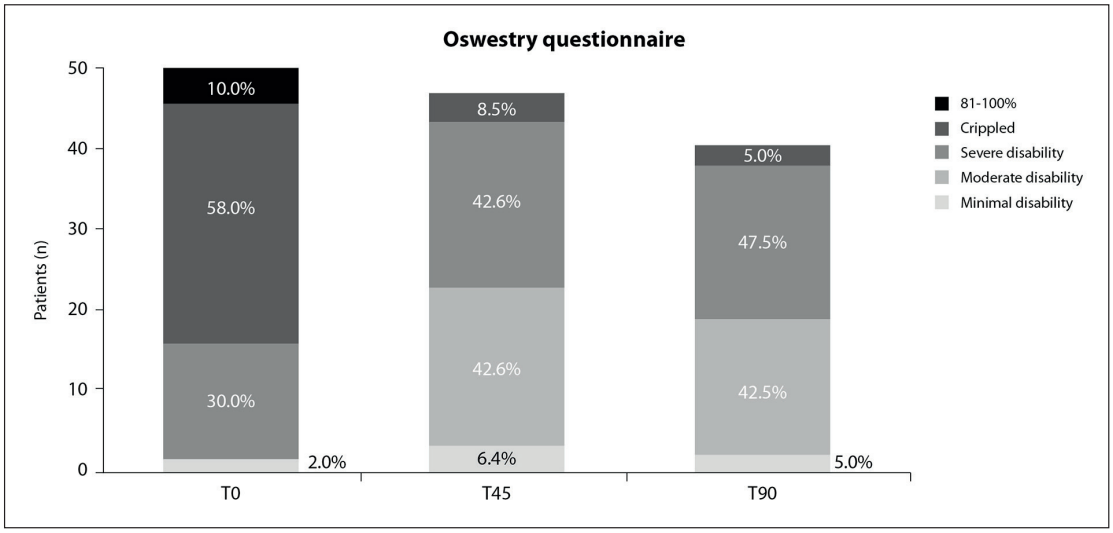

Figure 4. The Oswestry questionnaire assessing patients' disability throughout the study.

Sleep quality improved throughout the study (p<0.01), although the results of sleep quality evaluation are not available for all patients at each visit (Figure 2). Neuropathic symptoms were reported by 44 patients (88%) at T0. At T45, neuropathic symptoms were reduced to 21.3% with a further decrease to 15.4% at T90 (p<0.0001; Figure 3). The Oswestry questionnaire assigned a score to several items, which were subsequently matched to the corresponding degree of disability: minimal disability (0-20%); moderate disability (21-40%); severe disability (41-60%); crippled (61-80%); and complete disability (81-100%). At baseline, 68% of patients (34/50) had a severity score >60% (corresponding to crippled/complete disability); in 30% of patients (15/50) the score was between 40 and 60% (severe disability), with only one patient (2%) with a score below 40% (moderate disability). At T45, the percentage of patients with a score below 40% (minimum or moderate disability) improved to 49% (23/47 patients), with only 8.5% (4/47 patients) still above 60% (crippled/complete disability). At T90, previous results were confirmed: 47.5% of patients (19/40) were minimally disabled, with another 19/40 patients obtaining an intermediate score corresponding to severe disability, and only 2/40 patients (5.0%) with a score above 60% of complete disability. Thus, compared with baseline, the frequency of patients with a score corresponding to severe disability decreased significantly, both at T45 and at T90 (both p<0.01; Figure 4).

Adverse events were reported in 14 patients (28%). Of these, four patients (8%) discontinued therapy: one patient because of somnolence associated with moderate confusion, and three patients due to asthenia. Overall, tapentadol PR was very well tolerated in approximately 90% of the sample.

At T0, 98% of patients underwent RF, whereas this percentage dropped to 10% (five patients) at T45 and T90, with 86.4% of patients interrupting RF. The reduction is statistically significant (p<0.01).

Discussion

Recently, pain has been redefined as a combination of both sensory input evoked by inflammation or other diseases, and a multidimensional experience evoked by a neural network widely distributed in the brain[1,3,5,6]. Moreover, pain has multifactorial genesis, representing a unique individual patient experience highly variable during time, and thus therapy cannot be standardized universally. In accordance to this concept, pain management should be holistic and personalized according to each individual patient's needs. Notably, pain management should follow a multimodal approach, with both pharmacological and non-pharmacological options, according to pain intensity and pathophysiology, the complexity of symptoms, comorbidities, and the social context[12].

Furthermore, not all patients respond equally to the same treatment, and dose adaptations or switch to a different analgesic may be needed to achieve or maintain pain relief.

The WHO analgesic ladder has now been implemented with a fourth step, which consists of interventional approaches for the control of persistent neuropathic pain[19], in addition to the three basic steps of NSAIDs with/without other non-opioids (e.g., acetaminophen) for mild pain, mild opioids (e.g., codeine and tramadol) for moderate pain, and strong opioids (e.g., morphine, buprenorphine fentanyl, oxycodone and hydromorphone) in combination with/without non-opioids for severe pain[7,9].

Chronic pain can cause a substantial burden on healthcare systems and society, due to its high prevalence and economic costs[7-9]. As many as 19% of European adults report chronic pain of moderate to severe intensity, with frequently inadequate treatment[8,10].

Among the available options for the interventional management of pain, there are a variety of techniques, such as RF denervation and nerve blocks[12,20-23]. RF denervation consists in nerve ablation using heat generated by a continuous RF current, with high rates of clinical improvement. Pulsed RF, keeping the target nerve tissue at 42°C as temperature, is a less destructive treatment for dorsal root ganglion and for nucleus pulposus of intervertebral disc[24-26].

Tapentadol PR is comparable to, or even superior to, strong opioids for pain relief in moderate/severe chronic nociceptive and neuropathic pain conditions, with additional benefits on health status and quality of life[13-18]. Long-term pain relief for up to 2 years can be achieved and safely maintained for up to 4 years, without any signs of tolerance development[27,28]. Moreover, clinical trials and post-marketing experiences with tapentadol PR have shown its effectiveness for pain relief, associated to improvements of functionality, health status, and quality of life, as well as a good safety profile with, in particular, a more favorable gastrointestinal tolerability profile.

The risks connected to polypharmacy in the elderlies should be considered. The low potential for pharmacokinetic drug-drug interaction of tapentadol may represent a relevant aspect for therapy selection[29,30].

Our experience is the first of this type in a population of patients with chronic pain treated with radiofrequency. Chronic pain was highly prevalent among women, as reported elsewhere[7-10,31]. We obtained different rates of responders when considering two different thresholds for pain reduction. Notably, a 50% reduction in NRS score may represent a hard goal. However, our positive experience shows that the number of patients requiring additional non-pharmacological interventions such as RF, drops dramatically with tapentadol treatment. By combining pulsed RF and Tapentadol, we can achieve a synergism of analgesic effect on chronic lumbar radicular pain with less necessity of repeated RF and lesser doses of tapentadol. The overall good tolerability and safety of this medication have also been confirmed in our group of patients, with a limited number of adverse effects recorded.

Conclusions

Pain medicine has gained importance in the industrialized countries in which radiculopathy has become a major sanitary problem. At present, an innovative approach to treat chronic pain derived from radiculopathy consists in the combination of a wide-spectrum analgesic drug with pulsed RF, assuring rapid and effective management of chronic pain. The benefits of RF are rapid and persistent in approximately 60% of patients. The association of tapentadol PR with RF may represents a valid treatment option for chronic radicular pain. With its dual mechanism of action combining MOR and NRI, tapentadol is effective both on nociceptive and on neuropathic pain. The results of our study show that tapentadol PR is effective in reducing pain intensity at rest and during loading, with a favorable safety and tolerability profile. Moreover, the use of tapentadol PR decreases the degree and severity of disability, as well as the intensity of neuropathic symptoms. Noteworthy, during treatment with tapentadol the frequency of RF intervention may be reduced, with several patients not requiring any addition RF while on tapentadol.

Key Points

- Chronic pain involves structural plasticity of the affected tissues and is frequently irreversible. Frequently, a wide-range treatment approach for the treatment of chronic pain may include both analgesic drugs and interventional techniques such as radiofrequency.

- Continuous and pulsed radiofrequency are very effective in the management of radicular pain syndrome, leading to persisting benefits for 4 weeks and beyond. The pharmacological management of chronic radicular pain may be obtained with analgesics addressing both the nociceptive component and the neuropathic component of pain, such as tapentadol, in combination with radiofrequency.
- The dual mechanism of action of tapentadol, μ-opioid receptor agonist (MOR) and noradrenaline reuptake inhibitor (NRI), is effective both on nociceptive and neuropathic pain, with fewer side effects compared with opioids. Thus, tapentadol may be a favorable option for the treatment of chronic radicular pain in association with radiofrequency.
- Tapentadol PR showed a good overall efficacy and tolerability in our population of patients, with a statistically significant reduction in pain intensity both at rest and during loading compared with baseline ($p<0.0001$).
- Sleep quality, neuropathic symptoms, and the index of disability (Oswestry questionnaire) improved significantly throughout the study ($p<0.01$).
- A limited number of adverse events were reported, with only four patients requiring therapy discontinuation. Overall, tapentadol PR was very well tolerated in approximately 90% of the population sample.
- Radiofrequency was stopped in 86.4% of patients after the first intervention performed at baseline, with an optimal pain control obtained with tapentadol PR in most patients ($p<0.01$).

Conflict of interest

The authors declare no conflicts of interest.

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