

Article

Effectiveness of Combined Treatment Using Physical Exercise and Ultrasound-Guided Radiofrequency Ablation of Genicular Nerves in Patients with Knee Osteoarthritis

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Abstract: Radiofrequency (RF) is a mini-invasive neuromodulation intervention that is commonly used in chronic pain conditions including general musculoskeletal pain related to several diseases, including knee osteoarthritis (KOA). However, to date, few studies investigated synergistic therapeutic approaches combining RF with rehabilitative physical exercise protocols in KOA patients. This prospective cohort study aimed at assessing the short-term effects on pain in KOA patients of a multimodal intervention consisting of ultrasound (US)-guided RF geniculate ablation and concomitant rehabilitative physical exercise. We included grade III KOA patients with knee pain (Numerical Pain Rating Scale, NPRS >4) not responsive to conventional treatments. They underwent a combined intervention including US-guided RF geniculate ablation and a 2-week physical exercise program. At the baseline (T0) and 1 month after (T1) we assessed: NPRS, Knee Injury and Osteoarthritis Outcome Scale (KOOS), quality of life, exercise adherence, and safety. All the 47 KOA patients enrolled (68.8 ± 13.7 years old) showed a reduction of pain (NPRS: 7.48 ± 1.74; 3.63 ± 1.68; $p < 0.001$). In addition, there was a significant improvement ($p < 0.05$) also in the other functioning and HRQoL outcomes. Adherence to the exercise program was over 80% in more than half (28) of the patients. No major adverse events were reported. These findings suggested that US-guided RF ablation of genicular nerves combined with rehabilitative exercise therapy might be considered a safe and effective approach in the complex management of KOA patients.

Keywords: osteoarthritis; osteoarthritis; knee; radiofrequency ablation; pain; disability evaluation

1. Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease, characterized by progressive articular cartilage loss, formation of osteophytes, subchondral bone remodeling, and joint inflammation [1–3]. Knee OA (KOA) has a prevalence of 3.8% and an incidence of 12% in older patients and is characterized by joint pain and periarticular muscle weakness, with a subsequent loss of function, increased disability, lower performance in the activities of daily living (ADL), and reduction in health-related quality of life (HRQoL) [4,5]. Thus, an early diagnosis of OA is needed to better define the adequate therapeutic approach aimed at avoiding joint replacements [6].

Non-surgical treatments of symptomatic knee OA include rehabilitation interventions and pharmacological treatments, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids [7–9]. However, intra-articular injections with hyaluronic acid and glucocorticoids have been demonstrated to have a role in pain relief and recovering the viscoelastic properties of the synovial fluid and might be considered as a second-line approach in patients not responsive to acetaminophen and/or NSAIDs [7,10].

Furthermore, in recent years, there has been an increasing interest in other non-pharmacological treatments of KOA patients, including focal vibration [11], IA oxygen-ozone (O₂O₃) therapy [12–15], and radiofrequency (RF) ablation of genicular nerves [16–18].

This technique targets specific nerves producing a thermal lesion to the afferent sensitive nerve that interrupts nociceptive signals [19] and takes advantage of physical energy to treat chronic pain unresponsive to conservative therapies [20]. Thus, RF is considered a safe technique for patients with several comorbidities suffering critical painful conditions (e.g., trigeminal neuralgia, cancer pain, and spinal pain) [20], and has been recently proposed to treat severe KOA in patients not responsive to conservative management or not candidates for surgery [16–18].

Previous studies investigated the efficacy of percutaneous fluoroscopic-guided RF ablation performed on genicular nerves with promising results on pain and physical function [16,17]. However, RF use in KOA treatment is still limited, probably due to the small use of fluoroscopic guidance in rehabilitation clinical practice or the still low evidence in the scientific literature.

On the other hand, several papers [21–24] reported physical exercise as an effective non-pharmacological treatment in patients with chronic pain, with potential benefits in terms of self-reported pain, function, and consequent HRQoL in patients suffering from KOA. In contrast, several barriers to physical activity were identified, including fear of movement and pain during exercise that has been related to a lower adherence to an exercise program [25], with crucial implications in terms of treatment results. In this context, the effectiveness of therapy in KOA pain management might depend on exercise adherence, which should be promoted by physicians to perform an adequate and effective rehabilitative intervention.

However, to date, there is still a lack of evidence in the literature regarding specific strategies that could improve exercise compliance. Furthermore, to the best of our knowledge, there are no studies investigating the effects of multimodal interventions combining US-guided RF genicular ablation and specific rehabilitative exercise programs.

Therefore, this prospective cohort study aimed at assessing the safety, feasibility, and effectiveness of a comprehensive rehabilitative approach combining ultrasound (US)-guided RF ablation of genicular nerves and physical exercise therapy in reducing pain and improving HRQoL in KOA patients.

2. Materials and Methods

2.1. Participants

This prospective cohort study involved patients referred to the Pain Rehabilitation Outpatient Service, University Hospital “Maggiore della Carità”, Novara, Italy, from January 2019 to January 2020. The Inclusion criteria were the following: (a) age from 50 to 80 years old; (b) diagnosis of KOA according to the criteria recommended by the American College of Rheumatology (ACR) [26], grade III according to Kellgren–Lawrence classification [27]; (d) knee pain (Numeric Pain Rating Scale, NPRS, ≥ 4) lasting more than 3 months; (e) ineffective previous rehabilitative treatment and/or oral NSAIDs, corticosteroid, and analgesic drugs; (f) 1-week wash-out from oral analgesic drugs and NSAIDs before intervention; (g) 6-month wash-out period from previous intra-articular glucocorticoid treatment. The exclusion criteria were the following: (a) infection or skin lesions in the injection area; (b) knee ligaments’ lesions; (c) previous knee replacement or surgery; (d) femur or tibia/fibula fractures; (e) severe neutropenia; (f) allergy to anesthetic drugs; (g) clinical comorbidities and/or contraindications to physical exercise.

This study was approved by the Institutional Review Board and was performed in accordance with the Declaration of Helsinki [28] and pertinent National and International regulatory requirements. All the participants were asked to carefully read and sign an informed consent before collecting the data.

2.2. Intervention

The whole therapeutic intervention was characterized by the combination of US-guided RF genicular ablation and a rehabilitative physical exercise protocol.

After enrollment, all patients underwent RF with selective ablation of the supero-lateral, supero-medial, and infero-medial geniculate nerve. A US machine (Esaote My-LabSix, Genoa, Italy) was used to identify the genicular nerves that travel together with the genicular arteries in the neurovascular bundle. A 20 G specific needle was introduced percutaneously, and the correct positioning was confirmed by US guidance. A sensory test with 50 Hz and a motor test with 2 Hz was performed using an RF generator (Cosman G4, Burlington, MA, USA) to confirm the correct positioning of the cannula. The procedure was performed by the same expert physician under complete aseptic conditions. The nerve was anesthetized using a local anesthetic (2 mL lidocaine 2%) and a conventional RF thermocoagulation was performed with a temperature of 90 °C for 180 s [16]. The procedure was reproduced for each targeted nerve. Acetaminophen 1 g and topical cryotherapy were allowed if patients experienced pain in the treated region the day after the procedure. Moreover, peri-procedural and late complications were recorded.

All study participants started a 2-week physical therapy beginning the day after the procedure. All patients underwent five daily sessions per day for 2 weeks, supervised by an expert physical therapist. Each session lasted 30 min and consisted of three phases:

- Phase I (lasting 5 min): short warm-up including static and dynamic stretching exercises for knee flexor and extensor aimed at adapting the musculoskeletal system to the load and reduce the possibility of injuries.
- Phase II (lasting 20 min): resistance training characterized by isometric and isotonic exercises, including three free weight exercises (single leg raise, single leg extension on the chair, hip thrust), performed in 3 sets of 20 repetitions daily. Time under tension was set between 3 and 5 s in both concentric and eccentric contraction, while isometric contraction was set for 5 s. A one minute rest period was performed between each set.
- Phase III (lasting 5 min): cooling down including dynamic stretch exercises. After the exercise intervention, all patients were strongly encouraged to continue the training at home. Figure 1 depicts a study participant undergoing the physical exercise program.



Figure 1. Physical exercise performed by a study participant.

2.3. Outcome Measures

Demographic and anthropometric data were collected at the baseline (T0). The primary outcome of our study was the intensity of pain at rest, measured by NPRS. Secondary outcomes were: disability, assessed by the five different domains (symptoms, pain, ADL, function, and quality of life) of the Knee Injury and Osteoarthritis Outcome Score [29]; HRQoL, assessed by EuroQol Scales (EuroQol Five Dimensions, EQ-5D, and EuroQol Visual Analogue Scale, EQ-VAS) [30]; feasibility, assessed by the self-reported adherence to the physical exercise program; safety, measured recording peri-procedural or late complications. All the outcome measures were assessed at T0 and after 1 month (T1).

2.4. Statistical Analysis

Categorical variables were represented as numbers and ratios, whereas continuous variables were described as means $\pm$ standard deviations. Due to the small sample size, we supposed a non-Gaussian distribution of variables. Differences between each variable have been evaluated with Wilcoxon's signed-rank test. A *p*-value lower than 0.05 was considered as statistically significant. Descriptive statistics were used to summarize the adverse effect of the treatment. Statistical analysis was performed using Graphpad Prism 7.0 (GraphPad Software, Inc., San Diego, CA, USA).

3. Results

Out of 54 patients, 7 patients were excluded because they did not meet eligibility criteria (4 underwent previous surgery; 4 aged more than 80 years). Therefore, a total of 47 patients (mean aged 68.8 ± 13.7 years, body mass index: 28.2 ± 4.9 kg/m²) were included and their baseline characteristics are depicted in Table 1.

Table 1. Anamnestic and demographical characteristics of the study population.

	Patients (<i>n</i> = 47)
Age (years)	68.8 $\pm$ 13.7
BMI (kg/m ²)	28.2 $\pm$ 4.9
Sex (female/male)	28/19
Smoke (habitual smokers)	6 (12.7)
≥ 3 alcohol units/day	2 (4.2)
Caucasian ethnicity	45 (95.7)
Occupation (yes)	8 (14.9)

Continuous variables are expressed as means $\pm$ standard deviations, categorical variables are expressed as counts (percentages).

We observed a statistically significant reduction in pain at the 1-month evaluation (T1) (NPRS: 7.48 ± 1.74 vs. 3.63 ± 1.68 ; *p* < 0.001).

Moreover, all patients showed a significant decrease in disability at T1 as suggested by the reduction of KOOS score from 21.45 ± 7.33 to 44.97 ± 10.77 (*p* < 0.001). Considering the KOOS domains, there was a statistically significant difference at T1 (*p* < 0.001) in all except for the "symptoms domain" that did not significantly differ. In addition, a significant improvement in terms of HR-QoL was recorded in both EQ-5D (0.48 ± 0.06 vs. 0.67 ± 0.07 ; *p* < 0.001) and EQ-VAS (49.4 ± 4.3 vs. 79.4 ± 5.8 ; *p* < 0.001). Further details are shown in Figure 2.

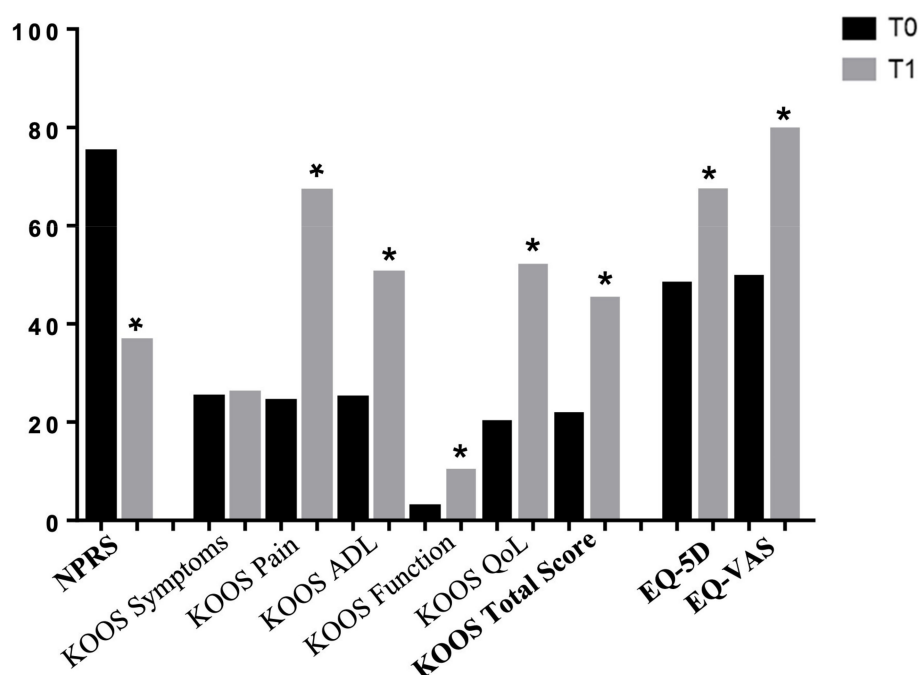


Figure 2. Differences between baseline (T0) and 1 month (T1) in the outcome measures ($n = 47$). Abbreviations: ADL: Activities of daily living; EQ-5D: EuroQoL Five Dimensions; EQ-VAS: EuroQoL Visual Analogue Scale; KOOS: Knee Injury and Osteoarthritis Outcome Score; NPRS: Numeric Pain Rating Scale; QoL: Quality of Life; T0: Baseline; T1: 1 Month after treatment.

Adherence to the exercise training program was over 80% of the sessions proposed in 28 participants. Furthermore, no major adverse events were reported, while few minor adverse events occurred as vagal reactions ($n = 2$), minor bleeding ($n = 17$), and temporary local hypoesthesia ($n = 29$). However, all these adverse events were self-limiting and did not require any medical intervention.

4. Discussion

In this pilot study, we showed that US-guided RF ablation of genicular nerves combined with physical exercise might be effective in reducing pain in patients affected by KOA in the short-term period. These results are intriguing considering the heavy burden of chronic pain that affects different domains of HRQoL and functioning and the lack of rapid and effective treatment strategies [16,17]. We observed a significant reduction in pain, with mean NPRS almost halved compared to baseline (7.48 vs. 3.63; $p < 0.005$) in just 2 weeks after the treatment. Moreover, our results are in line with those of Sari et al. [17] that in a recent RCT showed that the short-term effects of RF were significantly better compared to intraarticular glucocorticoid joint injection in KOA patients. Furthermore, in the present study, there was a significant improvement in physical function and ADL, as assessed by the improvement in all the KOOS domains. However, RF did not significantly change the KOOS “symptoms domain”, probably because it could not influence the pathophysiology of OA. On the other hand, our findings emphasize the positive effects of this combined RF and rehabilitative intervention in terms of pain, ADL, function, and quality of life subscales improvement and are in line with previous studies that assessed the positive role of RF on disability with similar outcome scales [16,31–33]. Lastly, this study confirmed that US-guided RF ablation of genicular nerves might be considered as a safe technique in KOA patients, as already assessed by previous studies [16,31]. In addition, our results reported for the first time the feasibility and the safety of a combined non-pharmacological treatment involving both US-guided RF geniculate ablation and physical exercise. Noticeably, it should be underlined that a US-guided cannula positioning is mandatory to perform a correct nerve ablation. A recent RCT [31] compared US-guided RF to fluoroscopy-guided RF

without finding any significant differences in terms of pain relief, functional improvement, and safety. US guidance could be considered as safer (no radiation exposure) and easy to use also in outpatient settings. Therefore, we confirmed the promising results previously described in the literature and support the US-guided RF as a useful and safe treatment for knee OA pain.

To date, the efficacy of physical exercise interventions on muscle strength and functional improvement in patients suffering from KOA is debated [21–24]. However, one of the most common factors negatively influencing physical exercise efficacy is knee pain that dramatically reduces the overall compliance to these interventions [25]. In the present study, US-guided RF treatment was proposed not only to reduce pain but also as a synergic and feasible intervention aiming at promoting physical exercise interventions in patients with KOA. To date, the European League Against Rheumatism and the ACR/Arthritis Foundation guidelines recommended lifestyle interventions to promote physical activity, involving multidisciplinary health professionals in a non-pharmacological approach [34,35]. However, the optimal approach to promote adherence to physical activity in patients suffering from KOA remains unclear.

In this scenario, our preliminary data showed promising results in reducing pain and improving functioning and HRQoL, suggesting that a comprehensive tailored approach focusing on early pain management could minimize the functional consequences of KOA, as previously reported in other chronic pain conditions [36–38].

In addition, recent advances in the understanding of the mechanisms underpinning pain chronicization reported that abnormal stimulations to the pain cortex areas might be involved in the abnormal responses that characterize chronic pain and are potentially linked to anxiety, depression, and sleep problems related to the stimulation of limbic region projections [39,40]. Therefore, a multidisciplinary intervention targeting different levels of pain circuits could play a pivotal role in patients not responding to conventional therapies, achieving significant improvements in both pain relief and HRQoL.

In light of these considerations, the positive results reported in the present study might be partially related to the multitarget effects that characterize the multimodal and combined therapeutic interventions and are in line with previous studies supporting the positive effects of physical exercise on HRQoL in several diseases [41–44].

Despite the promising results reported in the present study, several limitations should be noted: first, the lack of a control group, such as a placebo/sham treatment group or subjects undergoing other non-surgical interventions. Moreover, the short-term period of follow-up (1 month) did not allow for the assessment of the long-term effectiveness of the intervention and the duration of the positive results obtained. Lastly, the potential implications of RF in the risk of falls have not been investigated despite the damage to proprioceptive stimuli induced by genicular nerve ablation. On the other hand, functional improvement induced by physical exercise might have a role in mitigating the potential negative effects in proprioceptive stimuli transmission, supporting the synergic role of these techniques in the comprehensive treatment of KOA.

Furthermore, considering the lack of evidence in the scientific literature, this work provides promising data about a mini-invasive multimodal approach in KOA patients with chronic pain refractory to conventional therapies, including intra-articular injections. Moreover, to our knowledge, this is the first longitudinal study assessing the effects of US-guided RF genicular ablation combined with a rehabilitative exercise intervention in KOA patients.

5. Conclusions

Taken together, our findings suggested that US-guided RF ablation of genicular nerves combined with a rehabilitative exercise protocol might be considered as a safe and effective intervention to reduce pain and disability in patients affected by KOA not responsive to pharmacological treatments. These results suggest the positive role of rehabilitative interventions in chronic pain management in KOA, as previously described in different

musculoskeletal conditions. Moreover, the US guide has been confirmed as a useful, practical, and facilitating tool in performing this procedure. However, further studies are needed to confirm these results and to assess the long-term effects of RF ablation of genicular nerves combined with physical exercise in KOA patients.

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