Randomized Trial

# Bipolar Versus Unipolar Intraarticular Pulsed Radiofrequency Thermocoagulation in Chronic Knee Pain Treatment: A Prospective Randomized Trial

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**Background:** Chronic knee pain is a major widespread problem causing significant impairment of daily function. Pulsed radiofrequency has been shown to reduce severe chronic joint pain as a non-pharmacological and less invasive treatment method.

**Objective:** We aimed to compare the effectiveness of unipolar and bipolar intraarticular pulsed radiofrequency methods in chronic knee pain control.

**Study Design:** Prospective, randomized, double-blind study.

**Setting:** Pain clinic in Cukurova University Faculty of Medicine.

**Methods:** One hundred patients, aged 20 – 70 years with grade 2 or 3 knee osteoarthritis were included in this study. Patients were randomly allocated into 2 groups to receive either unipolar (group U, n = 50) or bipolar (group B, n = 50) intraarticular pulsed radiofrequency (IAPRF) with a 45 V voltage, 2 Hz frequency, 42° C temperature, 10 msec pulse width, and 10 minute duration. We recorded visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1) scores of patients at baseline and one, 4, and 12 weeks after the procedure. The primary outcome was the percentage of patients with ≥ 50% reduction in knee pain at 12 weeks after the procedure.

**Results:** There was a significant difference between the groups according to VAS scores at all post-intervention time points. In group B, 84% of patients, and in the group U, 50% of patients achieved at least 50% knee pain relief from the baseline to 3 months. In group B, WOMAC scores were significantly lower than the group U at one and 3 months.

**Limitations:** Lack of long-term clinical results and supportive laboratory tests.

**Conclusion:** Bipolar IAPRF is more advantageous in reducing chronic knee pain and functional recovery compared with unipolar IAPRF. Further studies with longer follow-up times, laboratory-based tests, and different generator settings are required to establish the clinical importance and well-defined mechanism of action of PRF.

This study protocol was registered at clinicaltrials.gov (identifier: NCT02141529), on May 15, 2014. Institutional Review Board (IRB) approval date: January 16, 2014, and number: 26/9

**Key words:** Chronic pain, intraarticular, knee joint, knee osteoarthritis, pain management, pulsed radiofrequency treatment, quality of life, recovery of function

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Osteoarthritis (OA) is one of the most common underlying causes of chronic knee pain resulting in loss of ability. Older age, female gender, overweight, prior knee injury, and having a positive family history are related risk factors for patients with OA (1-9). Chronic knee pain can be treated by physical therapy, non-steroid anti-inflammatory drugs (NSAIDs), tramadol, opioids, intraarticular hyaluronic acid, and steroids (10-13). Substantial improvements in pain control and functional recovery can be achieved by surgical interventions in patients with severe OA (10). Potential side effects of the drugs may not allow them to be used in patients having concomitant diseases. The unfavorable complications associated with an invasive surgical procedure such as infection, hematoma, or damage to the surrounding tissue should not be ignored. As an alternative technique, pulsed radiofrequency, a non-pharmacological and less invasive treatment method, can improve severe persistent joint pain (14-20). However, there are limited evidence-based data on the impact of pulsed radiofrequency on chronic knee pain. The majority of research in this particular area has been generally limited to retrospective analysis or case series.

Bipolar radiofrequency energy is locally produced between the active and grounding electrodes on needle tips, and unipolar radiofrequency energy exists between the intervention needle tip and a grounding plate. In a unipolar or bipolar mode, radiofrequency can be used to treat a painful joint (21-23). Bipolar radiofrequency has shown to produce electrical functionality for an effective electricity shift into the structures when compared with unipolar mode (24-26). In addition, there is no study assessing the efficacy of bipolar intraarticular pulsed radiofrequency (IAPRF) on knee OA pain.

Our study assessed whether there is a difference between bipolar IAPRF and unipolar IAPRF in reducing chronic knee pain. We hypothesized that bipolar IAPRF is a more efficient treatment to reduce pain compared with unipolar IAPRF. The primary endpoint was the pain level of patients with persistent knee pain 3 months after the intervention.

## Methods

After receiving written informed consent and Institutional Review Board approval (Date: January 16, 2014, and Number: 26/9), 100 patients aged 20 – 70 years with grade 2 or 3 OA according to the Kellgren–Lawrence classification, having knee pain over 3 months, were recruited to this prospective randomized double-blind study. Our study protocol was registered at clinicaltrials.gov (identifier: NCT02141529), on May 15, 2014. Exclusion criteria were chronic knee pain induced by infection, inflammation, tumors, and fractures or a history of acute knee pain, previous knee surgery, connective tissue diseases, neurologic or psychiatric disorders, the administration of steroids or hyaluronic acids within the last 3 months, coagulation disorders, and local infection of the site of intervention planned.

Patients are admitted to the preoperative unit 15 minutes before the procedure. After intravenous access was established by a 20-gauge cannula, all the patients were monitored by non-invasive blood pressure (NIBP), electrocardiogram (ECG), and peripheral oxygen saturation (SpO2) (Draeger-Primus Anesthesia Device Monitor, Draeger Medical Systems, Inc. 16 Electronics Avenue, Denver, MA 01923 USA) in the operating room before the intervention.

After patients were positioned supine, with a pillow placed to support the knee. An antero-posterior fluoroscopic image of the knee joint was obtained with C-arm fluoroscopy. A subcutaneous injection of lidocaine 1% of 2 mL was placed corresponding to the joint space on both of sides of the patellar ligament. Two radiofrequency electrode cannulas (10 cm length, 22-gauge, and 5 mm active tip) (NeuroTherm® RF Cannula) were bilaterally inserted at the medial and lateral sides of the patellar ligament for both groups (Fig. 1). Under fluoroscopic guidance, cannulas were advanced to the cavity of the knee joint at both the medial and lateral sites until the tips were in the middle of the joint space in the transverse plane (Fig. 2). We stopped the advancement of the cannulas in the sagittal plane when the tips were in the middle of the joint space in the transverse plane (Fig. 3). The distance between the 2 tips was adjusted to approximately 1 cm. Patients were randomly allocated into 2 groups in a 1:1 ratio by a computer-generated list. Radiofrequency generator (NeuroThermTM NT1000 RF Generator, Morgan Automation LTD. Liss, Hants, GU33 7NT, UK) settings were adjusted to a 45 V voltage, a 2 Hz frequency, a temperature of 42° C, a 10 ms pulse width, and a 10 minute duration by one staff member other than the practitioner who performed the intervention for each unipolar (group U) or bipolar (group B) PRF. The practitioner who performed all the interventions and patients were kept blind to the type of intervention. If there were no complications within one hour after the procedure, the patients were discharged. For supplemental analgesia, paracetamol 500 mg orally 4 times per day was recommended if patients had an uncomfortable

pain. If the patients had an intolerable pain, although taking paracetamol 4 times a day, the intervention was considered unsuccessful. An assessor staff blinded to the groups assessed the patients when they returned for clinical examination. We also called them by telephone for any further advice. We assessed the pain using a 10-cm visual analog scale (VAS). Zero identifies the least possible pain and 10 identifies the most severe pain imaginable. We tested the health status of patients by the Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1 (WOMAC) index, a valid and reliable self-administered questionnaire, including 24 items divided into 3 subscales (pain, stiffness, and physical function) (27). Higher scores indicate worse symptoms, more limitations, and poor health status. VAS and WOMAC scores were recorded at baseline and one, 4, and 12 weeks after the procedure. Supplemental analgesia requirements, any side effects, and complications such as a motor or sensory loss were also noted at the same time points after the procedure.

The primary outcome was the percentage of patients with ≥ 50% reduction in knee pain measured by VAS walking on flat ground at 3 months after the procedure. Additional analyzes were done on the quality of life and the functional response to treatment using WOMAC at the same time points.

## Statistical Analysis

The sample size was calculated according to a 2-arm pilot study including 10 patients in each group. We found that 80% of patients in the bipolar treatment group achieved the primary outcome versus 50% of the unipolar treatment group. Based on a power of 80% and a 2-tailed alpha of 0.05, we calculated a

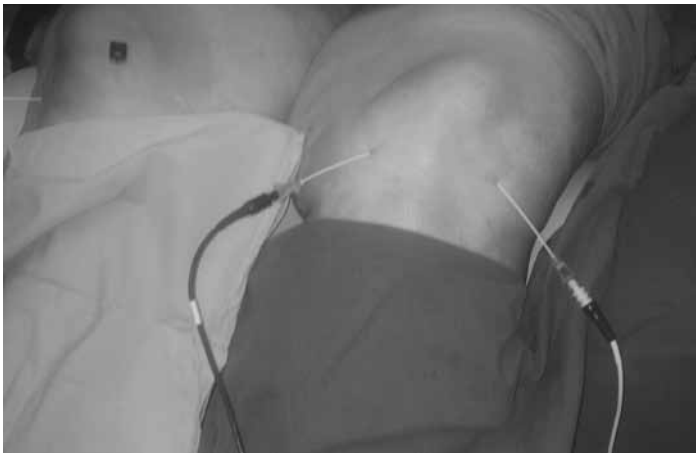

Fig. 1. *The placement of radiofrequency electrodes at medial and lateral sides of the patellar ligament.*

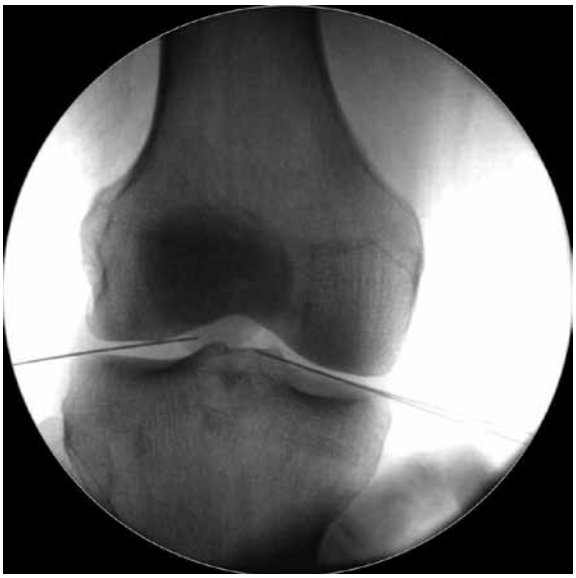

Fig. 2. *Fluoroscopic image of anteroposterior view of the knee joint. RF cannulas were bilaterally placed into the cavity of the knee joint.*

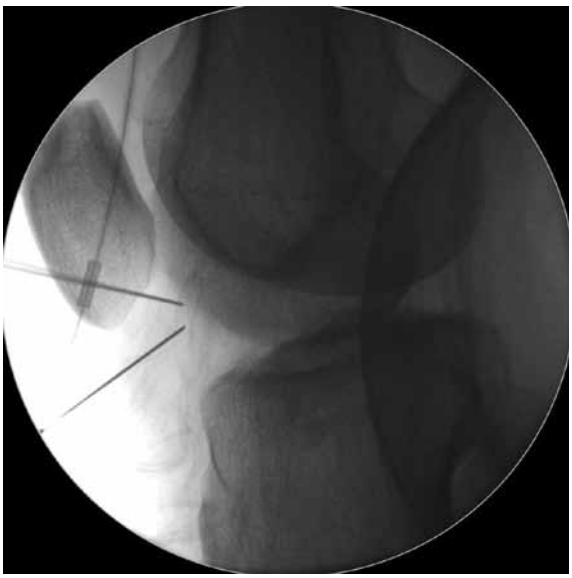

Fig. 3. *The lateral fluoroscopic view of the knee joint with 2 radiofrequency electrodes in joint space.*

sample size as 44 patients in each group. We recruited 50 patients per group to compensate for potential dropouts. IBM SPSS 22.0 package program was used in statistical analysis. All variables were evaluated using the visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to test whether they were normally distributed. Categorical measurements were demonstrated in the number and percentage, and continuous measurements were represented as mean, standard deviation, median, and minimum-maximum. Chi-square test or Fisher's exact test was used to analyze the categorical variables (i.e., gender, intervention site, Kellgren–Lawrence grade). To compare the difference between the groups, the independent-samples t-test was used for analysis of normally distributed data (i.e., age, height, and BMI) and the Mann-Whitney U test was used for non-normally distributed data (i.e., VAS and WOMAC scores). The changes of VAS and WOMAC scores were also measured comparing scores across baseline, one week, one month, and 3 months using Friedman's test and post-hoc multiple comparisons by Wilcoxon signed-rank test due to violations of parametric test assumptions (non-normal distribution). A *P*-value of $< 0.05$ was considered statistically significant.

## Results

We recruited 113 patients for our study and included 100 of them with chronic knee pain; 13 were unable to meet the study inclusion criteria. One hundred patients fulfilled the inclusion criteria (Fig. 4). Thus, we performed a statistical analysis using data from 100

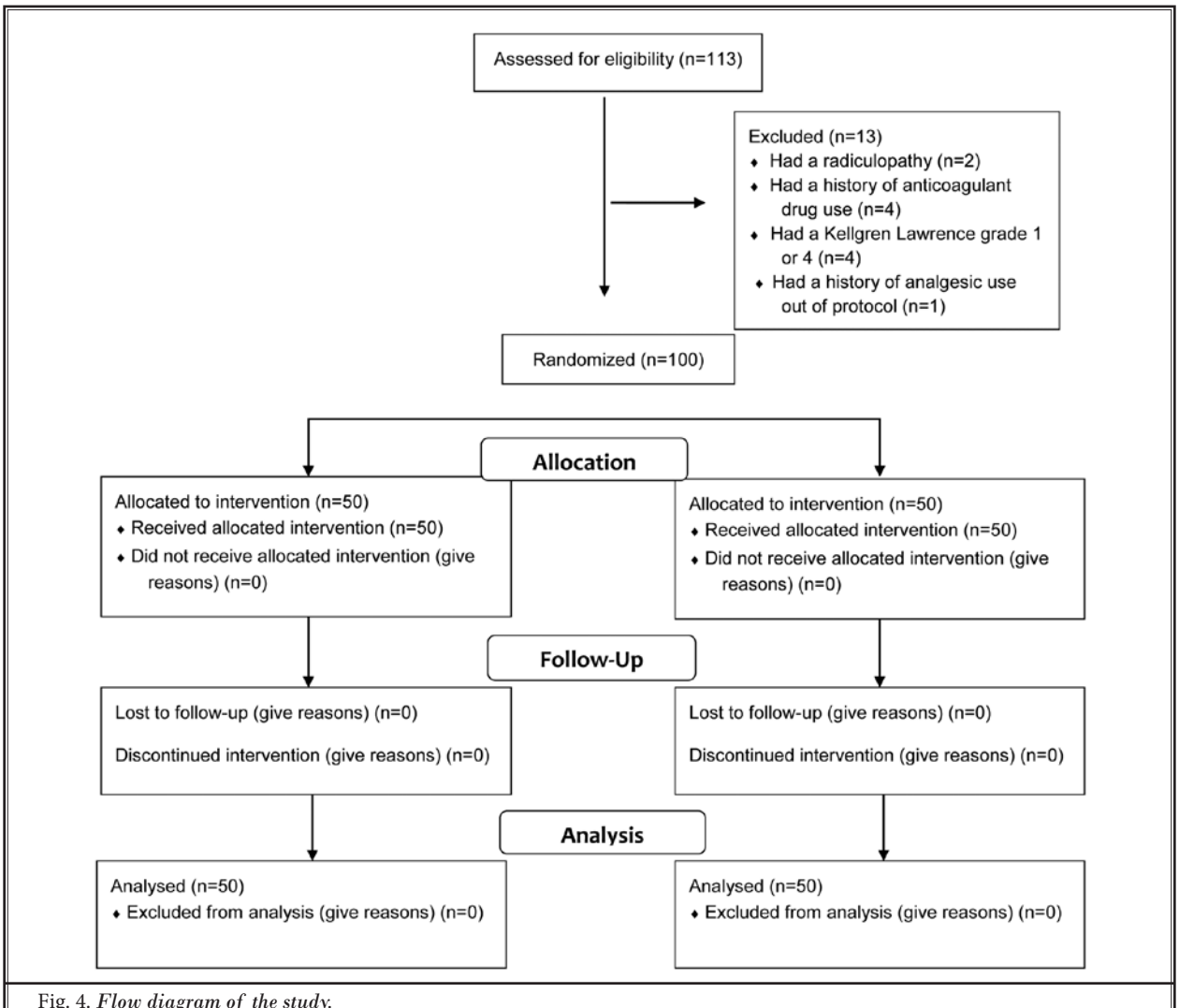


Fig. 4. *Flow diagram of the study.*

patients (n = 50, group B and n = 50, group U) for the study. Baseline characteristics of the groups were similar (Table 1).

## Primary Outcomes

There was a significant difference between the groups according to VAS scores at all post-intervention time points. Forty-two patients (84%) in group B and 25 patients (50%) in group U achieved at least 50% knee pain relief from the baseline to 3 months (Fig. 5). VAS scores were significantly lower at all post-intervention time points than the baseline in both groups (Fig. 6).

Table 1. *Demographic data and clinical characteristics of patients.*

| | Group B | Group U | Total | *P* value |
|---|---|---|---|---|
| Age (years) | 63.6 ± 5.9 | 64.1 ± 5.7 | | 0.653[a] |
| Gender | | | | |
| Male | 17 (34%) | 20 (40%) | 37 (37%) | 0.534[c] |
| Female | 33 (66%) | 30 (60%) | 63 (63%) | |
| Weight (kg) | 81.0 (70.0 – 95.0) | 81.0 (67.0 – 90.0) | | 0.576[b] |
| Height (m) | 1.66 ± 0.1 | 1.64 ± 0.1 | | 0.106[a] |
| BMI (kg/m$^2$) | 29.4 ± 2.0 | 29.9 ± 2.0 | | 0.164[a] |
| Kellgren–Lawrence grade | | | | |
| 2 | 26 (52%) | 28 (56%) | 54 (54%) | 0.688[c] |
| 3 | 24 (48%) | 22 (44%) | 46 (46%) | |
| Site of intervention | | | | |
| Right | 28 (56%) | 27 (54%) | 55 (55%) | 0.841[c] |
| Left | 22 (44%) | 23 (46%) | 45 (45%) | |
| Duration of OA (years) | 5 (3 – 9) | 4 (3 – 8) | | 0.569[b] |

a. Independent T-Test was used for variables normally distributed. B. Mann-Whitney-U was used for non-normally distributed data. C. Chi-square test was used for categorical data. Values represent mean and standard deviation for age, height, BMI, and median (min – max) for weight and duration of OA (osteoarthritis). Categorical data of gender, Kellgren–Lawrence grade and the site of intervention represent the number of cases and percentage (%) within group. BMI, body mass index. Group B, patients treated using bipolar intraarticular PRF. Group U, patients treated using unipolar intraarticular PRF.

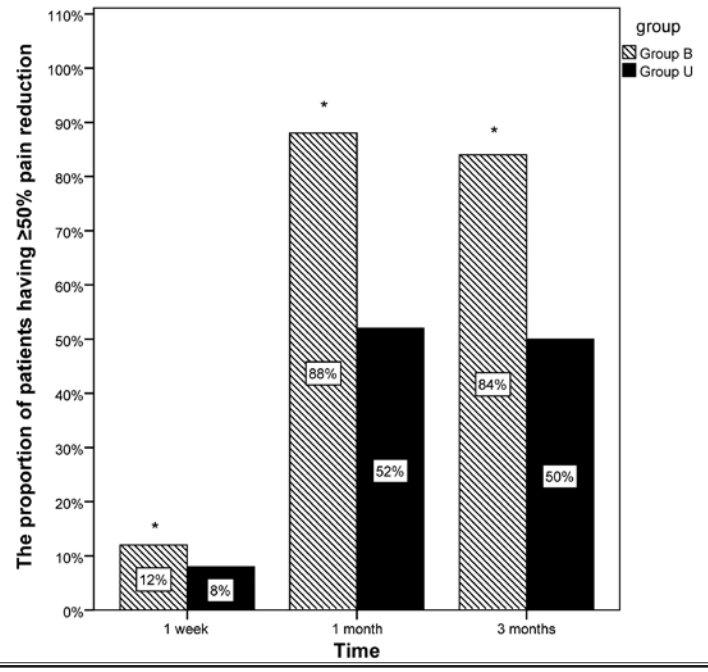


Fig. 5. *The proportion of patients having at least 50% reduction in knee pain. Group B patients received bipolar pulsed radiofrequency. Group U patients received unipolar pulsed radiofrequency. *P < 0.05, compared with group U.*

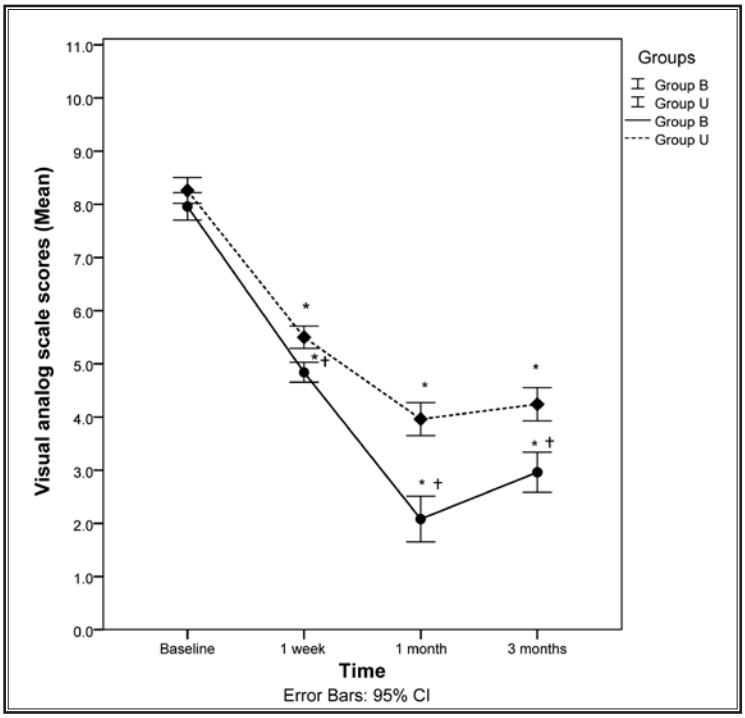


Fig. 6. *Visual analogue scale pain scores in patients treated with intraarticular pulsed radiofrequency. Group B patients received bipolar pulsed radiofrequency. Group U patients received unipolar pulsed radiofrequency. Values represent mean and standard deviation. *P < 0.05 compared with baseline value. †P < 0.05 compared with group U.*

## Secondary Outcomes

WOMAC scores in group B were significantly lower compared with group U at one and 3 months (Table 2). WOMAC scores were significantly lower at all post-intervention time points than the baseline in both groups (Table 2). There was no report of side effects after the intervention. The rates of patients requiring supplemental analgesic within group B vs group U were 94.0% vs 84.0%, 18.0% vs 26.0%, and 16.0% vs 28.0% at one week, one month, and 3 months, respectively.

Table 2. *WOMAC scores of the groups.*

| WOMAC | Group B | | Group U | | *P* value |
|---|---|---|---|---|---|
| | Mean ± SD | Median (Min – Max) | Mean ± SD | Median (Min – Max) | |
| **Baseline** | | | | | |
| Pain | 15.6 ± 1.7 | 15.0 (12.0 – 20.0) | 16.0 ± 1.6 | 16.0 (13.0 – 19.0) | 0.131 |
| Stiffness | 4.7 ± 0.8 | 5.0 (3.0 – 6.0) | 4.7 ± 0.7 | 5.0 (3.0 – 6.0) | 1.000 |
| Function | 43.4 ± 3.0 | 43.0 (39.0 – 52.0) | 43.9 ± 2.7 | 43.0 (38.0 – 52.0) | 0.232 |
| Total | 63.7 ± 4.4 | 63.0 (57.0 – 73.0) | 64.6 ± 2.8 | 64.0 (59.0 – 72.0) | 0.154 |
| **1 week** | | | | | |
| Pain | 10.3 ± 1.1 | 10.0 (8.0 – 12.0) | 10.6 ± 1.0 | 11.0 (9.0 – 12.0) | 0.279 |
| Stiffness | 3.6 ± 0.7 | 4.0 (2.0 – 5.0) | 3.7 ± 0.8 | 4.0(2.0 – 5.0) | 0.609 |
| Function | 30.1 ± 3.3 | 30.0 (25.0 – 36.0) | 30.5 ± 1.6 | 30.0 (27.0 – 35.0) | 0.538 |
| Total | 44.1 ± 3.3 | 44.0 (38.0 – 50.0)† | 44.8 ± 1.8 | 45.0 (41.0 – 48.0)† | 0.292 |
| **1 month** | | | | | |
| Pain | 4.4 ± 0.7 | 4.0 (3.0 – 6.0)* | 4.9 ± 0.8 | 5.0 (3.0 – 6.0) | 0.001 |
| Stiffness | 2.7 ± 0.6 | 3.0 (2.0 – 4.0) | 2.8 ± 0.5 | 3.0 (2.0 – 4.0) | 0.105 |
| Function | 7.2 ± 1.1 | 7.0 (5.0 – 10.0) | 7.7 ± 0.8 | 8.0 (6.0 – 9.0) | 0.231 |
| Total | 14.3 ± 1.3 | 14.4 (12.0 – 17.0)*† | 15.4 ± 1.4 | 15.0 (12.0 – 19.0)† | 0.002 |
| **3 months** | | | | | |
| Pain | 5.0 ± 1.1 | 5.0 (3.0 – 8.0)* | 6.7 ± 1.1 | 7.0 (4.0 – 8.0) | < 0.001 |
| Stiffness | 2.0 ± 0.6 | 2.0 (1.0 – 3.0)* | 2.3 ± 0.6 | 2.0 (1.0 – 4.0) | 0.009 |
| Function | 8.0 ± 1.8 | 8.0 (5.0 – 12.0)* | 9.4 ± 1.1 | 9.0 (7.0 – 12.0) | < 0.001 |
| Total | 14.9 ± 1.6 | 15.0 (12.0 – 18.0)*† | 18.3 ± 1.8 | 18.0 (15.0 – 22.0)† | < 0.001 |

**P* < 0.05 compared with group U. Mann-Whitney U test was used for WOMAC data analysis. †P < 0.001 compared with baseline WOMAC total scores. WOMAC. Western Ontario and McMaster Universities Osteoarthritis Index LK

There is a significant decrease in the number of weekly supplemental analgesic use in one and 3 months compared with the first week, but no difference between one and 3 months' values (Fig. 7).

## Discussion

In this study, we show that bipolar IAPRF reduces chronic OA pain more than unipolar PRF. To our knowledge, this is the first prospective randomized study to examine the effect of the IAPRF technique on a chronic knee joint pain. IAPRF has been suggested to reduce chronic pain in the knee OA. Masala et al (28) showed a decrease in prolonged knee pain after performing IAPRF with 45 V and pulse width of 20 ms during 10 minutes by one electrode. A retrospective study described a percentage of ≥ 50% pain reduction in 35.5% of cases using one electrode PRF with 45 V and pulse width of 20 ms during 15 minutes (14). Another retrospective analysis Schianchi et al (18) demonstrated significant pain reduction of long duration in patients with knee joint pain using an IAPRF with 60 V and pulse width of 5 – 10 ms during 15 minutes. A case report of 6 cases demonstrated a pain-free period for 10 months after receiving IAPRF with a pulse width of 10 ms and 60 V for knee pain (19). The other method used for knee pain, genicular RF neurotomy, which is applied to articular nerves around the knee joint, improves pain control and functional ability in patients with OA knee pain (29). Genicular RF neurotomy is a neuroablative technique in which the electrode tip temperature is increased to 70 – 80°C.

Although PRF is a potent non-pharmacological method for several pain conditions, it is still unknown which mechanisms provide the pain-reducing effect of PRF (19,30,31). However, laboratory data show that PRF is a neurobiological real event with variations in pain signals as a neuromodulator characteristic (20). The generated electric field in PRF is responsible for ensuring analgesia rather than changes in the temperature of nerves (32). PRF, unlike the conventional radiofrequency technique, can be used on peripheral nerves and joint spaces. Although debate continues that PRF may have an effect of structural damage in tissue around the electrode (33-35), there is no clinical evidence of that. PRF decreases the pain in several joints such as cervical facet, knee, shoulder, sacroiliac, atlantoaxial, and radiocarpal. Two mechanisms are advocated for its pain-reducing effect; first, the inhibition of excitatory C-fibers and synaptic transmission, mainly in a small joint and the second is on the immune cells, which clarifies the effects on large joints such as the shoulder and the knee. The generated electric field attenuates the pro-inflammatory cytokines such as interleukin-1β, tumor necrosis factor-α, and interleukin-6 by influencing the immune cells. Therefore, the intervention causes a major response rather than a restricted tissue effect

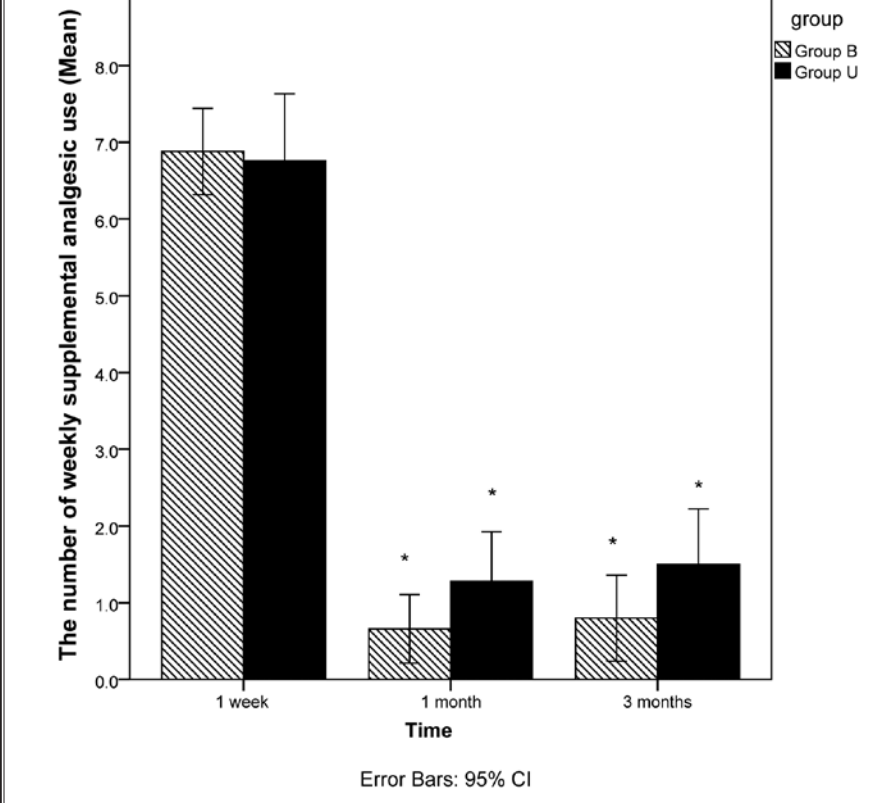


Fig. 7. *The amount of weekly supplemental analgesic use over time. *P < 0.05 compared with first week value. CI, confidential interval.*

(19,30,36). Moffet et al (37) investigated the effect of PRF on the modulation of peripheral analgesia using human dermal fibroblasts and human epidermal keratinocyte cultures and showed an increasing effect of PRF on the mRNA of endogenous opioid precursors (pro-enkephalin, pro-opiomelanocortin, pro-dynorphin) and corresponding opioid peptides. PRF may have a cartilage-protective or regenerative effect. An electric field exposure produces chondrocyte proliferation and matrix synthesis (38-42), and we argue, therefore, that if PRF is applied into the joint space, such a regenerative response is more likely to be achieved than those in peripheral nerve supplies of the knee.

The tissue areas affected by bipolar RF can be more pervasive than those of unipolar RF (43,44). However, there is no reliable evidence that bipolar PRF has a stronger effect on the tissue compared with unipolar PRF. Previous studies investigated the effects of IAPRF interventions on the knee joints; however, none of them included the 2-sided application. The knee has a larger joint space; and hence, we expected that if we use 2 electrodes for IAPRF, a greater articular surface area can be affected than those with one electrode. The other reason for using 2 electrodes is that bipolar PRF requires 2 electrodes. We could not find a significant reduction in pain at one week after the intervention for either unipolar or bipolar PRF. However, we determined a pain-reducing effect of PRF at one month and after that. We assumed that the PRF could not directly influence the surrounding nociceptive nerve endings. That late onset of action of PRF may be due to the increased distance between the electrode tip and the articular surface or a possible delayed response depending on the affected production of pro-inflammatory cytokines. The distance between 2 electrode tips, the duration of intervention, pulse width, the voltage applied, the inter-tip angle, and parallel inter-tip offset can greatly influence the dimension of the thermal lesion field. However, the electric field may be more extensive than that dimension (44,45). If a higher voltage is applied, it may be expected to produce a greater electric field in the joint space and if so, it is reasonable to use a voltage over 45 V for larger joints such as the shoulder and knee.

This study add to the information about IAPRF by providing data on the advantages of bipolar PRF compared to unipolar PRF. However, some important limitations need to be considered. The current study did not include a no-treatment control group, using the same intervention without activation of the RF generator. Considering the potential benefits of IAPRF, as control patients could not be benefit from any medication except for PRF treatment, we did not include a control group in this study. The lack of change over time in patients' weights limits our study. The weight alterations of patients during 3 months may be a confounding factor influencing our results because weight is a factor influencing knee pain. Lack of long-term results limits our ability to determine the difference between the 2 methods over a long-term period. Further data collection is required to show a difference between the 2 methods in terms of long-term effects. WOMAC is a self-report tool, and although we used the Turkish validated version of the WOMAC, patients may have reporting bias because difficulty in understanding the questionnaire due to sociocultural factors. Another weakness is that there was no laboratory testing for the estimation of pro-inflammatory mediators or tissue damage markers such as the degradation biomarker of collagen type II (CTX-II) in the blood sample.

## Conclusion

In conclusion, although both methods are efficacious, bipolar IAPRF is a more effective treatment in reducing chronic knee pain compared with unipolar IAPRF. Prospective randomized controlled studies with long-term follow-ups, laboratory-based tests, and different generator settings should be performed to show a more detailed action mechanism for IAPRF.

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