Randomized Controlled Trial

A Double-Blind, Placebo-Controlled Study of Ultrasound-Guided Pulsed Radiofrequency Treatment of the Saphenous Nerve for Refractory Osteoarthritis-Associated Knee Pain

Hironobu Uematsu, MD, PhD[1], Seiichi Osako, MD[1], Saya Hakata, MD, PhD[1], Daijiro Kabata, MPH[2], Ayumi Shintani, PhD[2], Daiki Kawazoe, BS[3], Kiyonori Mizuno, MD, PhD[3], Yuji Fujino, MD, PhD[1], and Yoichi Matsuda, MD, PhD[1]

From: [1]Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Suita, Japan; [2]Department of Medical Statistics, Osaka City University Graduate School of Medicine, Osaka, Japan; [3]Anshin Clinic, Kobe, Japan

Address Correspondence:
Hironobu Uematsu, MD, PhD
Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine
2-2 Yamadaoka, Suita
Osaka, 565-0871, Japan
E-mail: Uhironobu@anes.med.osaka-u.ac.jp

Disclaimer: Funding for this study was obtained (Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine) from St. Jude Medical (n/k/a Abbott Medical).

Conflict of interest: This study was conducted with funding (Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine) from St. Jude Medical (n/k/a Abbott Medical), the company that sells the NT500 device (Neuro Thermo®) used in the study. Information obtained in the course of this study: was not disclosed while the study was ongoing; will only be used for scholarly purposes, such as announcements in scholarly meetings or research papers; and will not be used in commercial advertising and the like by St. Jude Medical (n/k/a Abbott Medical) that might pose any conflicts of interes.

Manuscript received: 10-19-2020
Revised manuscript received: 03-15-2021
Accepted for publication: 03-19-2021

Free full manuscript: www.painphysicianjournal.com

Background: While the efficacy of pulsed radiofrequency (PRF) for shoulder pain has been demonstrated, its efficacy on the saphenous nerves for knee osteoarthritis (OA)-associated pain has only been reported in observational studies.

Objectives: The aim of this study was to compare saphenous nerve PRF to placebo for knee OA-associated pain.

Study Design: Patients, practitioners, and outcome assessor-blinded randomized placebo-controlled trial.

Setting: Pain management clinics at 2 hospitals in Japan.

Methods: Patients were randomly allocated to the PRF (n = 37) or placebo group (n = 33). Patients aged 40-85 years with refractory anteromedial knee pain. PRF in the saphenous nerve under ultrasound guidance. The placebo group underwent the same procedure, but with motor stimulation. The primary endpoint was the average pain intensity measured using the visual analog scale (VAS) at the 12-week post-treatment visit; secondary outcomes included the average VAS at 1 and 4 weeks, and pain intensities at rest, in flexion, at standing, and at walking. Other secondary outcomes were knee pain, symptoms, activities of daily living, knee-related quality of life, mobility, range of motion, and adverse events.

Results: In the PRF group, the mean VAS score was 52.41 ± 26.17 at 12 weeks, while in the sham group, the mean VAS score was 63.06 ± 27.12 ($P < 0.05$). There were no significant differences between the groups in any of the secondary outcomes.

Limitations: Patients with comorbidities were excluded from this study. The follow-up time was limited to 12 weeks.

Conclusions: Ultrasound-guided saphenous nerve PRF proved to be effective for at least 12 weeks in patients with knee OA and showed no adverse events.

Key words: Pulsed radiofrequency treatment, knee osteoarthritis, saphenous nerve, ultrasound-guided, randomized controlled trial, pain, pain management, placebo

Pain Physician 2021: 24:E761-E769

Knee osteoarthritis (OA) is a progressive locomotor pain disease that frequently causes joint pain. Knee OA-associated refractory pain arises soon after OA onset due to damage and deformation of the knee joint, gradually impairing everyday activities, such as walking. There are an estimated 24 million people with knee OA in Japan (1), of whom 8.2 million have knee pain. Furthermore, according to results from the 2013 Comprehensive Survey of Living Conditions conducted by Japan's Ministry of Health, Labour and Welfare (2), knee OA and other joint diseases affect the healthy life expectancy of the elderly and are a major risk factor for requiring long-term care.

The recommended treatment for knee OA is conservative therapy (3,4), consisting of parallel administration of drug treatments (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen, etc.) and nondrug therapies (e.g., muscle strength training, rehabilitation therapy, etc.). However, in many cases, drug treatments have little effect, with many patients discontinuing drug intake due to gastrointestinal problems and other side effects. Moreover, nondrug therapies are not fully implemented in many patients due to pain. Total knee arthroplasty (TKA) and other surgical treatments are performed in serious cases, although these surgical interventions are associated with numerous problems. High-risk patients with comorbidities are contraindicated for surgery, and approximately 40% of patients who undergo surgery develop persistent postoperative pain (5). Roughly 80,000 TKAs are performed per year in Japan, which accounts for approximately 1% of the total number of cases of knee OA (1,2). As such, many patients with knee OA either continue to receive conservative treatments for many years or live with profound impediments to their daily life activities, while experiencing pain. Japan's population has become increasingly aged, with a growing population at high risk of knee OA. Therefore, there is an urgent need for new, safe, and effective treatment methods that can be implemented in most patients.

Recent advances in radiofrequency (RF) thermocoagulation devices have seen the development of pulsed radiofrequency (PRF) (5,6) as a safer and more minimally invasive treatment for pain, with PRF now being adopted to treat different types of refractory pain, particularly cervical radiculopathy. PRF is an analgesic technique that delivers intermittent RF currents, maintaining a safe temperature that does not \damage living tissue (≤ 42°C), while affecting nerves using an electric field. In contrast to conventional RF thermocoagulation, which is neurodestructive, PRF has a low likelihood of damaging nerves or peripheral tissues (7) and is unlikely to cause paresthesia or muscular weakness.

PRF is covered by health insurance in Japan for all types of chronic pain, including facial pain, neck pain, and lower back pain, and is used clinically on a variety of different nerves. To date, many clinical studies on the analgesic effect of PRF have demonstrated its long-term efficacy (3-6 months) (6) for various types of refractory pain, with most focusing on neuropathic pain. Three randomized controlled trials (RCTs) (8-10) examined shoulder joint pain, in particular, and have demonstrated: 1) an effect equivalent or superior to conventional nerve block treatment or intraarticular steroid injections, which persisted for at least 12 weeks after a single implementation; and 2) additional utility in improving impaired function when used in combination with rehabilitation therapy. However, no RCTs have been conducted to demonstrate that PRF on nerves is clinically effective for knee OA-associated pain compared with a placebo.

The saphenous nerve is the longest sensory nerve that branches from the femoral nerve and is one of the nerves that control the knee joint. After branching from the femoral nerve, the saphenous nerve passes along the adductor canal together with the femoral artery and vein, and after reaching the posterior of the medial condyle, it branches into the infrapatellar branch and medial crural cutaneous branch. The saphenous nerve is thought to give off a branch to the knee joint near its medial side (11), which controls sensory perception in the inferior medial side of the knee joint. Consequently, the saphenous nerve is thought to be implicated in pain in the inferior medial section of the knee joint, which is most commonly associated with knee OA. For perioperative pain relief for TKA, an ultrasound-guided saphenous nerve block in the adductor canal provides equivalent or superior pain relief compared with abdominal epidural anesthesia or a femoral nerve block (12,13). Akbas et al (14) conducted a retrospective study on 115 patients with knee OA and reported a significant decrease in pain intensity at 10 days, 3 months, and 6 months after PRF was applied to the knee joint branch given off by the saphenous nerve. Based on the above, we hypothesized that applying PRF to the saphenous nerve under ultrasound guidance would be an effective treatment for knee OA-associated pain, particularly for pain in the inferior medial part of the joint.

While the long-term efficacy and safety of PRF on nerves for shoulder joint pain has been demonstrated in RCTs, the efficacy of PRF on the saphenous nerves for knee OA-associated pain has only been reported in observational studies. The objective of this study was to conduct a double-blind, placebo-controlled study of ultrasound-guided PRF on the saphenous nerve in patients with knee OA and refractory knee pain, and to investigate the efficacy and safety of this procedure.

Methods

Study Design

We performed a patient-, practitioner-, and outcome assessor-blinded, 2-arm, parallel-group, randomized, placebo-controlled trial for 12 weeks. Patients with knee OA were recruited from the Center for Pain Management of Osaka University Hospital and the Anshin Clinic via posters or advertisements from April 2016 to March 2018. All outcomes were assessed at baseline and at 1, 4, and 12 weeks after treatment. This trial was preregistered with the University Hospital Medical Information Network, Clinical Trial Registry (UMIN-CTR) in Japan, ID: UMIN000022736. A detailed protocol is available from the authors upon request.

Patients

Patients, aged 40-85 years, with anteromedial knee pain were examined to ascertain their eligibility. After clinical and radiologic assessment, the study comprised patients with refractory knee pain of moderate intensity or greater for at least 3 months before the study (score of ≥ 40 mm on a 0-100 mm visual analog scale [VAS]) and with a radiographic confirmation of a clinical diagnosis of tibiofemoral OA (Kellgren-Lawrence grades 2-4). In these patients, knee pain did not respond to conservative treatments, including oral analgesics, exercise, strength training, and intraarticular injection with steroids or hyaluronic acids. Exclusion criteria included acute pain, serious psychiatric or neurologic disorders, connective tissue diseases affecting the knee, current use of anticoagulant medications and pacemakers, prior knee surgery, and intraarticular injection with steroids or hyaluronic acids within the past 3 months.

Interventions

The patients in the PRF group received PRF in the supine position under ultrasound guidance. In the mid-thigh region, a practitioner identified the saphenous nerve deep within the adductor canal to the sartorius muscle in a short-axis view (Fig. 1). Under sterile conditions, the skin and soft tissues were anesthetized with 1 mL of 1% lidocaine, and a 100 mm, 22-gauge RF cannula with a 5 mm active tip was inserted until the tip touched the saphenous nerve. Subsequently, a 100 mm RF electrode, which was connected to an RF generator (JK3 or NT500, Neuro Thermo®, Abbott Medical, Japan), was inserted through the cannula. Sensory stimulation (100 Hz, 0.3 V) was performed to identify the infrapatellar branch of the saphenous nerve, and motor stimulation (3 Hz, 0.5 V) was performed to avoid activation of the motor nerves to the vastus medialis. If stimulation could not be achieved below the knee (in

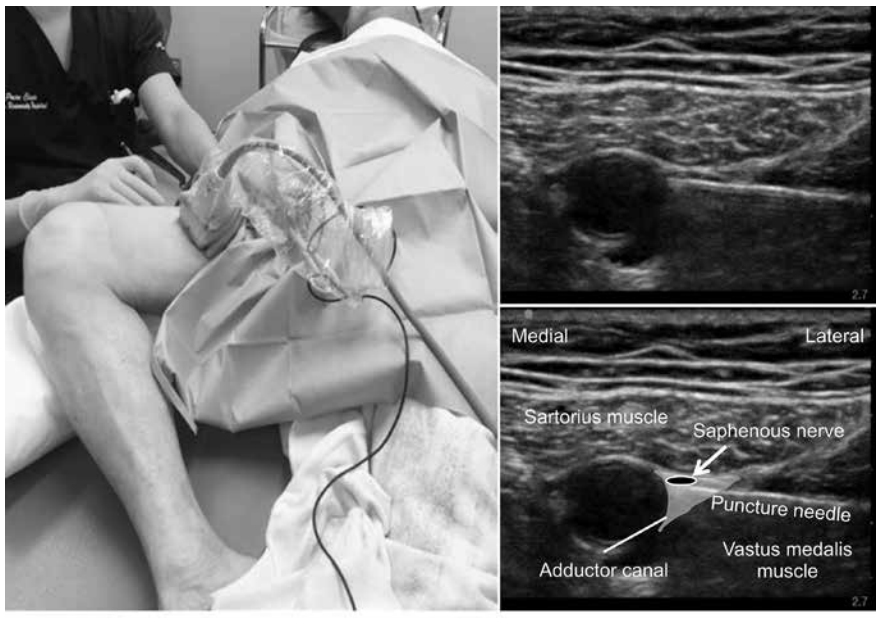

Fig. 1. *Ultrasound-guided pulsed radiofrequency on the saphenous nerve: a) position of the ultrasound nerve and puncture site, and b) ultrasound images.*

the region innervated by the infrapatellar branch) or if there was contraction of the vastus medialis muscle, the electrode inside the needle was advanced carefully under the sartorius muscle until it came into contact with the saphenous nerve, and stimulation was felt below the knee. After confirming stimulation below the knee without contraction of the vastus medialis muscle, PRF was performed 4 times using a current of 2 Hz, periods of 20 ms, and at a temperature of 42°C for 120 s. The patients in the placebo group underwent the same procedure with motor stimulation (3 Hz, 0.5 V) for 120 s, which was repeated 4 times. Patients were instructed to rest for the remainder of the day of the procedure and to keep the puncture site clean. Patients were instructed not to change their oral medication for the duration of the study.

Outcomes

All outcomes were measured at baseline and at 1, 4, and 12 weeks after the procedure. Because we expected the maximal clinical effect of PRF on the saphenous nerve for knee pain to be observable 12 weeks post-treatment, we chose the primary endpoint as the average pain intensity measured using the VAS at the 12-week visit. The secondary outcomes included the average VAS at 1 and 4 weeks, and pain intensities at rest, in flexion, at standing, and at walking, as measured using the VAS. Other secondary outcomes were: knee pain; presence of symptoms; activities of daily living; knee-related quality of life (QOL), measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS); mobility, measured using the time up and go test (TUG); knee function, measured using the range of motion (ROM) of the knee; and any adverse events during the treatment period. There were no changes in the trial outcomes after the trial commenced.

Sample Size

The number of patients was calculated based on pilot data and a t test comparing mean pain on a numerical rating scale (NRS-11) between the 2 groups. The standard deviation (SD) of change in NRS-11 among patients was 2.167, according to the pilot data. Given that -1.5 was a clinically significant difference in NRS-11 between the 2 groups, a sample size of 45 patients in each group was needed to maintain a test power of 90% with a 2-sided significance level of 5%. Assuming a 10% dropout rate, a sample size of 50 patients was needed in each group. The sample size (15) was calculated using the PS Power and Sample Size software.

Randomization and Blinding

After screening, all included patients were randomly allocated to a PRF or placebo group using the replacement block method. Two strata were defined based on the VAS at the initial assessment ($\geq$ 40 mm and < 70 mm; $\geq$ 70 mm and $\leq$ 100 mm), and stratification was performed using the REDcap® system. All interventional procedures were performed by a blinded practitioner (H.U.). Attending investigators, patients, outcome assessors, and data analysts were blinded to the study. The randomization sequence was prepared by a research assistant (K.S.) with no clinical involvement in this study. The allocation was concealed in a computer file that was only accessible to the research assistant throughout the study. Individual allocations were held in sealed, opaque, and consecutively numbered envelopes. The envelopes were opened sequentially by nonblinded research collaborators who operated the RF generator. Because patients experienced a similar twitching sensation during PRF and motor stimulation, the patients were not aware of the type of procedures performed.

Statistical Methods

To assess the effect of PRF on the VAS 12 weeks after the interventional procedure, which was the primary outcome, we performed a multivariable linear regression analysis with the VAS measured at 12 weeks as a function of the PRF group variable. Adjustments were made to account for the VAS measured before the interventional procedure, and the patients' height and weight. Similar analyses were conducted for the following secondary outcomes: VAS (one week and one month after the interventional procedure), knee ROM, TUG test, and KOOS. Missing values (n = 1, by dropout) were imputed using a multiple imputation method. All hypothesis tests were conducted at a 2-sided, 5% significance level using R software (www.r-project.org/foundation).

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Osaka University Clinical Research Review Committee (Approval numbers: 15607 and T15607). Written informed consent was obtained from all the patients.

Results

Patient Flow and Recruitment

Between April 2016 and March 2018, a total of 76 eligible patients were screened. Six patients were ex-

cluded; therefore, 70 patients were randomly allocated to either the PRF (n = 37) or the placebo group (n = 33), and comprised the intention-to-treat population (Fig. 2). Excluded patients included 3 who declined to participate, one with a scheduled varix surgery during our study period, one with radicular pain, and one with severe lumbago. After 4 weeks, none of the patients in either group dropped out. However, after 12 weeks, one patient in the placebo group dropped out of the study because she began taking duloxetine.

Baseline Data

The baseline characteristics are summarized in Table 1. The median ages of the treatment and placebo groups were 73 and 74 years, respectively; 76% and 85% of the treatment and placebo groups, respectively, were women. The median body mass index (BMI) in the treatment and placebo groups was 26 and 24, respectively. There were many patients with advanced knee deformation, with 13 (35%) and 15 (46%) patients in the treatment and placebo groups classified under the Grade 4 Kellgren-Lawrence condition (Table 1). The KOOS subscale scores measured before PRF were as follows: 44.4 treatment, 36.1 placebo for KOOS Pain (0-100%, higher value indicates normality) median 51.5 treatment, 52.9 placebo for KOOS ADL, and 25.0 in both groups for KOOS QOL, which meant that most patients had a moderate or higher degree of pain and had severe impairments in ADL and QOL.

Primary Outcome

The change in the VAS score is shown in Fig. 3. In the sham group, the mean VAS score was 69.49 ± 17.74 (mean ± SD) at baseline, which decreased to 52.55 ± 27.05 at one week, and gradually increased at 4 and 12 weeks (56.12 ± 29.06, 63.06 ± 27.12, respectively). In the PRF group, the mean VAS score at baseline was 71.68 ± 13.84 , which gradually decreased at 1 and 4 weeks (53.41 ± 23.35 and 48.16 ± 25.76, respectively), and was almost maintained at 12 weeks (52.41 ± 26.17). There was a significant difference between the 2 groups in the mean score of the average VAS at 12 weeks (Table 2).

Ancillary Analyses

There were no significant differences between the groups in any of the secondary outcomes, including VAS at rest, in flexion, at standing, or at walking, and the TUG, ROM, or KOOS subscales (Table 2).

Harms

No serious complications, such as paresthesia or muscle weakness, occurred in either group during the study. Subcutaneous bleeding associated with needle puncture was observed in one patient in the sham group, but the wound rapidly healed without any adverse effects.

Discussion

Similar to previous reports (14), PRF performed on the infrapatellar branch of the saphenous nerve in this study proved efficacious for 12 weeks for intractable knee pain associated with knee OA, without involving any paresthesia or muscle weakness throughout the course of treatment. Previous reports on saphenous nerve PRF in patients with knee OA adopted methods

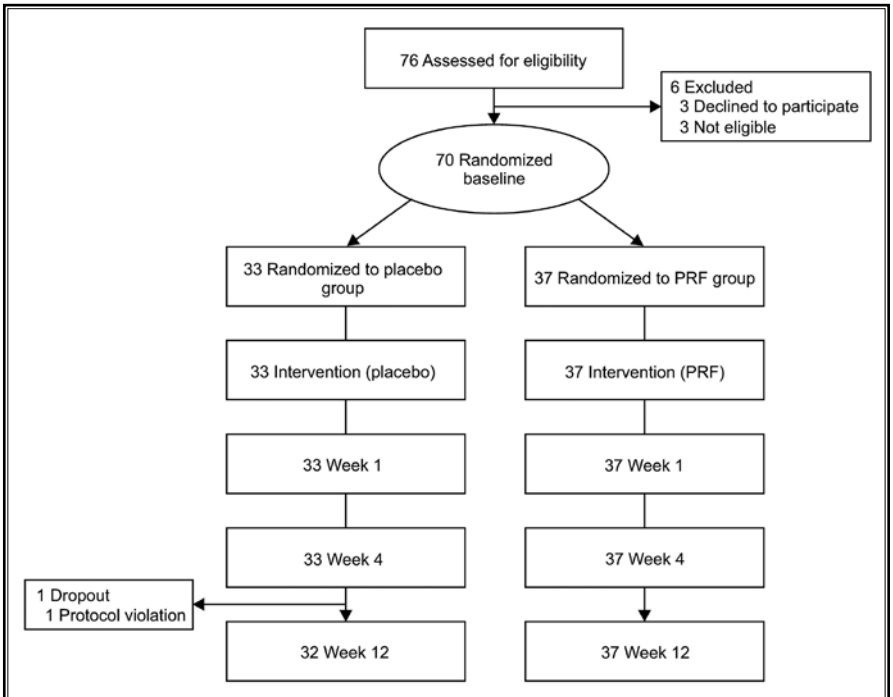

Fig. 2. *Study flowchart.*

Table 1. *Baseline characteristics and values for primary and secondary outcomes.*

	Level	Placebo	PRF	Overall	Missing (%)
n	-	33	37	70	-
Age at Enrollment (Median [IQR])	-	74.30 [68.85, 77.37]	73.05 [67.80, 77.92]	73.73 [67.99, 77.62]	-
Gender (1 = male) % (freq)	-	84.8 (28)	75.7 (28)	80.0 (56)	-
	1	15.2 (5)	24.3 (9)	20.0 (14)	
Enrolling Site % (freq)	Anshin Clinic	9.1 (3)	10.8 (4)	10.0 (7)	-
	Osaka University Hospital	90.9 (30)	89.2 (33)	90.0 (63)	
Height (Median [IQR])	-	155.00 [150.00, 159.00]	153.00 [150.00, 160.00]	154.00 [150.00, 159.00]	-
Weight (Median [IQR])	-	59.00 [53.00, 65.80]	62.80 [55.00, 75.00]	60.50 [54.50, 67.75]	-
BMI (Median [IQR])	-	24.44 [21.92, 26.94]	25.99 [23.88, 28.44]	25.16 [22.74, 27.65]	-
Kellgren-Lawrence % (freq)	II	27.3 (9)	18.9 (7)	22.9 (16)	-
	III	27.3 (9)	45.9 (17)	37.1 (26)	
	IV	45.5 (15)	35.1 (13)	40.0 (28)	
Average VAS at Enrollment (Median [IQR])	-	70.00 [56.00, 82.00]	75.00 [64.00, 81.00]	73.50 [61.25, 81.75]	-
ROM in Flexion at Enrollment (Median [IQR])	-	120.00 [110.00, 135.00]	120.00 [110.00, 125.00]	120.00 [110.00, 130.00]	-
ROM in Extension at Enrollment (Median [IQR])	-	0.00 [-10.00, 0.00]	0.00 [-10.00, 0.00]	0.00 [-10.00, 0.00]	-
Timed Up and Go Test at Enrollment (Median [IQR])	-	10.51 [9.23, 13.65]	9.58 [8.40, 12.95]	10.10 [8.69, 13.36]	-
KOOS ADL at Enrollment (Median [IQR])	-	52.94 [39.71, 69.12]	51.47 [48.53, 63.24]	52.21 [45.59, 67.65]	-
KOOS Pain at Enrollment (Median [IQR])	-	36.11 [30.56, 52.78]	44.44 [38.89, 55.56]	41.67 [33.33, 54.86]	-
KOOS QOL at Enrollment (Median [IQR])	-	25.00 [12.50, 31.25]	25.00 [6.25, 31.25]	25.00 [12.50, 31.25]	-
KOOS Sports at Enrollment (Median [IQR])	-	20.00 [10.00, 30.00]	25.00 [15.00, 35.00]	20.00 [15.00, 35.00]	-
KOOS Symptom at Enrollment (Median [IQR])	-	46.43 [32.14, 60.71]	50.00 [42.86, 57.14]	46.43 [35.71, 57.14]	-

Abbreviations: PRF, pulse radiofrequency; IQR, interquartile range; BMI, body mass index; VAS, visual analog scale; ROM, range of motion; KOOS, knee injury and osteoarthritis outcome score; ADL, activities of daily living; QOL, quality of life.

to approach the nerve with the needle blindly (14,16), which carries the risk of physically damaging the nerve or the surrounding blood vessels. In contrast to cryoneurolysis, which has been shown to result in significant pain reduction (17) but is neurodestructive, the ultrasound-guided saphenous nerve PRF used in this study was able to easily visualize the nerve, surrounding vessels, and the needle, which helped to avoid the risk of vessel puncture and nerve damage. This can, therefore, be regarded as a safer method than the conventional saphenous nerve PRF, which is performed in blindly. The PRF used in the present study maintains the needle tip temperature at a safe level (< 42°C) to ensure that it does not deform the nerve or surrounding tissues and, consequently, is highly unlikely to cause nerve damage (6). The ultrasound-guided saphenous nerve PRF used in the present study is similar to cryoneurolysis and blinded saphenous nerve PRF in that a single session of treatment is effective in reducing pain associated with knee OA over a long period of time, although one considerable difference is that it is safer than the 2 former approaches.

In PRF, the electric field generated at the needle tip influences the nerves, although how the electro-

magnetic waves affect the targeted nerve and bring about an analgesic effect is yet to be fully elucidated. Animal experiments using electron microscopes have shown that the electric field generated at the needle tip reversibly changes the fine structure of axons in neurons, and these changes are more profound in finer Aδ fibers and C fibers than in Aβ fibers (18). Furthermore, electrophysiological experiments have shown that PRF selectively blocks nerve activity in C fibers (19). These findings suggest that PRF has no effect on thick nerve fibers involved in movement and sense of touch, but affects the thin nociceptive fibers alone; thus, PRF brings about a long-term analgesic effect by suppressing their activity, without causing muscle weakness or paresthesia. However, although PRF is regarded as a safe method, it may cause nerve damage when performed for a long period of time and should, therefore, be performed with care. In this study, PRF was performed over the longest possible duration (8 min) that, according to previous reports, does not lead to adverse events (14). As mentioned, none of the patients displayed symptoms indicative of nerve damage. However, further studies are needed to establish the optimal PRF time for each targeted nerve. In addition, hypotheses on the mechanism of action of PRF are not limited to the peripheral mechanism, as discussed above. It has been suggested that mechanisms that affect central nervous system plasticity, such as suppression of microglial activity in the posterior horn of the spinal cord (20) and intervention of the descending pain inhibitory pathway (21), may be involved. Further studies to elucidate the mechanism of analgesia by PRF are needed.

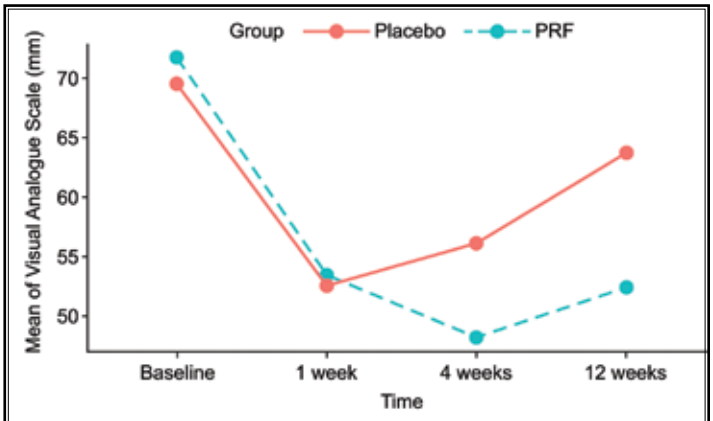

Fig. 3. *Scores using the VAS of the pulsed radiofrequency and placebo groups over 12 weeks post-treatment in a randomized controlled trial of Japanese patients with knee osteoarthritis (n = 70).*

Table 2. *Primary and secondary outcomes and differences between the groups.*

	Week 1		Week 4		Week 12	
	Mean Difference (95% CI)	***P* value**	**Mean Difference (95% CI)**	***P* value**	**Mean Difference (95% CI)**	***P* value**
Average VAS (0-100)	-0.799 (-11.190 to 9.592)	0.878	-9.311 (-20.814 to 2.192)	0.111	-11.658 (-23.124 to -0.193)	0.046
VAS (0-100)						
Rest	-4.186 (-15.428 to 7.057)	0.460	1.268 (-11.222 to 13.758)	0.840	-5.352 (-18.882 to 8.178)	0.432
Flex	2.561 (-12.218 to 17.339)	0.730	-1.048 (-16.561 to 14.464)	0.893	-5.200 (-17.535 to 7.136)	0.403
Stand	-2.945 (-14.549 to 8.659)	0.614	-1.097 (-13.938 to 11.743)	0.865	-13.549 (-26.647 to -0.451)	0.043
Walk	-3.245 (-13.923 to 7.433)	0.546	-8.924 (-21.174 to 3.327)	0.151	-12.734 (-24.731 to -0.738)	0.038
TUG (sec)	-0.157 (-1.078 to 0.764)	0.735	-0.278 (-1.242 to 0.687)	0.567	-0.808 (-2.978 to 1.363)	0.460
ROM (degree)						
Flexion	2.865 (-3.038 to 8.768)	0.336	-3.263 (-10.221 to 3.695)	0.352	1.778 (-4.884 to 8.441)	0.596
Extension	-0.969 (-3.056 to 1.118)	0.357	0.191 (-1.907 to 2.289)	0.856	-0.138 (-2.567 to 2.291)	0.910
KOOS subscales						
Pain	1.317 (-5.775 to 8.409)	0.712	1.229 (-6.444 to 8.902)	0.750	4.816 (-3.848 to 13.481)	0.271
ADL	0.866 (-4.935 to 6.667)	0.767	0.142 (-6.077 to 6.362)	0.964	1.013 (-5.882 to 7.907)	0.770
QOL	0.165 (-6.934 to 7.263)	0.963	0.784 (-6.516 to 8.084)	0.831	-0.489 (-7.957 to 6.978)	0.896
Sports / Rec	-3.421 (-10.882 to 4.040)	0.363	1.172 (-7.573 to 9.917)	0.790	-3.173 (-11.038 to 4.692)	0.423
Symptom	1.600 (-5.598 to 8.798)	0.659	3.295 (-4.155 to 10.745)	0.380	3.080 (-4.825 to 10.985)	0.43

Abbreviations: VAS, visual analog scale; TUG, time up and go; KOOS, knee injury and osteoarthritis outcome score; ROM, range of motion; ADL, activities of daily living; QOL, quality of life.

PRF is particularly appealing as a treatment because alternative treatments have several limitations. Pharmacotherapy often produces short-term improvements and leaves patients with inadequate pain control. The intraarticular injection of hyaluronic acid, which is commonly used as a treatment for knee OA in Japan, is only effective for a short period of time; therefore, patients are forced to visit hospitals frequently to receive treatments. Moreover, because the upper limit of insurance coverage is 1 or 2 injections per month, patients are often forced to spend most of the conservative treatment period in pain. Furthermore, risks of bleeding and infection associated with intraarticular injections that are otherwise low with single injections can increase to nonnegligible levels when injections are administered frequently. In contrast, a single session of saphenous nerve PRF can be expected to provide at least 12 weeks of analgesic effects. This helps patients avoid the risks of bleeding and infection associated with frequent needle punctures, and cut costs associated with frequent hospital visits and intraarticular injections. Moreover, although this study did not include patients engaging in rehabilitation, exercise, or muscle training in parallel with PRF, we believe that patients who respond well to PRF can spend a longer period of time free from pain, which could enhance the effect of such training methods that are essential for the treatment of chronic joint diseases. Future studies should examine the combined effect of rehabilitation, exercise, and muscle training alongside PRF, which may lead to prolonged and clear functional improvements. This may potentially prolong the healthy life expectancy of elderly individuals, thereby reducing the need for caregiving and providing economic benefits.

Limitations and Generalizability

Limitations of the study include the relatively small sample size, limited number of sites, and homogeneity of the population. Patients with comorbidities were excluded, and the follow-up time was limited to 12 weeks. In addition, absolute declines in pain were relatively small, and no differences were detected in the KOOS, QOL, or ADL scales.

Conclusions

Ultrasound-guided saphenous nerve PRF proved to be effective for at least 12 weeks in patients with knee OA, and showed no adverse effects that might suggest nerve damage. Although we were able to show that a single session of treatment can result in long-term improvements in pain, the observation period of this study was limited to 12 weeks; therefore, there is a need for further prolonged prospective studies to determine the duration of the therapeutic effect. Given the demonstrated safety and efficacy of the treatment for other conditions, we anticipate that saphenous nerve PRF will become commonplace in clinical practice as a treatment for patients with knee OA.

Acknowledgments

We would like to extend our gratitude to Tetsuya Tomita, MD, PhD (Department of Orthopedic Biomaterial Science, Osaka University Graduate School of Medicine) for his help recruiting patients. Editorial support, in the form of medical writing, table assembly, creation of high-resolution images based on authors' detailed directions, collating author comments, copyediting, fact-checking, and referencing, was provided by Editage, Cactus Communications, and funded by St. Jude Medical (n/k/a Abbott Medical).

Unblinded Statements

Patients with knee osteoarthritis were recruited from the Center for Pain Management of Osaka University Hospital and the Anshin Clinic via poster or advertisement from April 2016 to March 2018.

Ethical Approval/Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Osaka University Clinical Research Review Committee (Approval numbers: 15607 and T15607). All patients provided written informed consent.

Trial Registration

This trial was preregistered with the University Hospital Medical Information Network, Clinical Trial Registry (UMIN-CTR) in Japan, ID: UMIN000022736.

References

1. Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: The research on osteoarthritis/osteoporosis against disability study. *J Bone Miner Metab* 2009; 27:620-628.
2. Ministry of Health Labour and Welfare. Accessed February 8, 2021. www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa13/index.html
3. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2020; 72:149-162.
4. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019; 27:1578-1589.
5. Wylde V, Hewlett S, Learmonth ID, et al. Persistent pain after joint replacement: Prevalence, sensory qualities, and postoperative determinants. *Pain* 2011; 152:566-572.
6. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: Mechanisms and potential indications - a review. *Acta Neurochir (Wien)* 2011; 153:763-771.
7. Cosman ER Jr, Cosman ER Sr. Electric and thermal field effects in tissue around radiofrequency electrodes. *Pain Med* 2005; 6:405-424.
8. Wu YT, Ho CW, Chen YL, et al. Ultrasound-Guided pulsed radiofrequency stimulation of the suprascapular nerve for adhesive capsulitis: A prospective, randomized, controlled trial. *Anesth Analg* 2014; 119:686-692.
9. Eyigor C, Eyigor S, Korkmaz OK, et al. Intra-Articular corticosteroid injections versus pulsed radiofrequency in painful shoulder: A prospective, randomized, single-blinded study. *Clin J Pain* 2010; 26:386-392.
10. Gofeld M, Restrepo-Garces CE, Theodore BR, et al. Pulsed radiofrequency of suprascapular nerve for chronic shoulder pain: A randomized double-blind active placebo-controlled study. *Pain Pract* 2013; 13:96-103.
11. Horner G, Dellon AL. Innervation of the human knee joint and implications for surgery. *Clin Orthop Relat Res* 1994; 301:221-226.
12. Jæger P, Zaric D, Fomsgaard JS, et al. Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty: A randomized, double-blind study. *Reg Anesth Pain* Med 2013; 38:526-532.
13. Chan EY, Fransen M, Parker DA, et al. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. *Cochrane Database Syst Rev* 2014; 2014:Cd009941.
14. Akbas M, Luleci N, Dere K, et al. Efficacy of pulsed radiofrequency treatment on the saphenous nerve in patients with chronic knee pain. *J Back Musculoskelet Rehabil* 2011; 24:77-82.
15. Dupont WD, Plummer WD Jr. Power and sample size calculations: A review and computer program. *Control Clin Trials* 1990; 11:116-128.
16. Baysal PK, Baysal Ö, Erkılınç A, et al. Is saphenous nerve radio frequency an effective treatment for advanced gonarthrosis in elders with cardiac comorbidity? *J Back Musculoskelet Rehabil* 2018; 31:113-118.
17. Radnovich R, Scott D, Patel AT, et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: A multicenter, randomized, double-blind, sham-controlled trial. *Osteoarthritis Cartilage* 2017; 25:1247-1256.
18. Erdine S, Bilir A, Cosman ER, et al. Ultrastructural changes in axons following exposure to pulsed radiofrequency fields. *Pain Pract* 2009; 9:407-417.
19. Huang RY, Liao CC, Tsai SY, et al. Rapid and delayed effects of pulsed radiofrequency on neuropathic pain: Electrophysiological, molecular, and behavioral evidence supporting long-term depression. *Pain Physician* 2017; 20:E269-e283.
20. Park HW, Ahn SH, Son JY, et al. Pulsed radiofrequency application reduced mechanical hypersensitivity and microglial expression in neuropathic pain model. *Pain Med* 2012; 13:1227-1234.
21. Hagiwara S, Iwasaka H, Takeshima N, et al. Mechanisms of analgesic action of pulsed radiofrequency on adjuvant-induced pain in the rat: Roles of descending adrenergic and serotonergic systems. *Eur J Pain* 2009; 13:249-252.