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A randomized controlled study of the long-term efficacy of cooled and monopolar radiofrequency ablation for the treatment of chronic pain related to knee osteoarthritis

Ricardo Vallejo [a,b], Ramsin Benyamin [a], Jorge Orduña-Valls [c,d], Alejandro Vallejo [a,e], Samuel M. Thomas [a,f], David L. Cedeño [a,b,*]

[a] Millennium Pain Center, 2406 E. Empire St., Bloomington, IL, 61704, USA
[b] Lumbrera Research, 33 Derby Way, Bloomington, IL, 61704, USA
[c] Hospital Quirón Salud Valencia, Av. de Blasco Ibáñez, 14, 46010, Valencia, Spain
[d] Hospital Clínico Universitario de Valencia, Av. de Blasco Ibáñez, 17, 46010, Valencia, Spain
[e] Midwestern University, 555 31st Street, Downers Grove, IL, 60515, USA
[f] College of Osteopathic Medicine, Munroe, 3200 Grand Ave, Des Moines, IA, 50312, USA

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ABSTRACT

Background: Chronic knee pain due to osteoarthritis (OA) is expected to become more prevalent. Although conventional therapies may provide relief they are not long-lasting. Persistent pain may lead to total knee replacement, which is not free of adverse outcomes. Monopolar and cooled radiofrequency ablation (RFA) of genicular nerves is an effective option. However, either method may provide distinctive results depending on expected lesion size, a key aspect considering the anatomical variability of knee innervations. This prospective, double-blind, randomized controlled trial evaluated the efficacy and durability of knee RFA using a cooled probe or a monopolar probe of comparable diameter.

Methods: This investigator-initiated, post-market, double-blinded, prospective, randomized controlled trial was approved by the Western IRB. 79 subjects with chronic knee pain due to knee OA were enrolled in multiple locations of a single center. 75 subjects were randomized (1:1) into RFA treatment with either a 4 mm/17G cooled active tip (CRFA) or a 10 mm/16G monopolar active tip (MRFA) using conventional procedures. Primary endpoint was change in knee pain level (100 mm VAS score) from baseline at 24-week post-treatment. Other endpoints include change in functionality, global perceived effect, and frequency of adverse events. Evaluation spanned to 52-week post-treatment. Significance of results ($p < 0.05$) was calculated using standard statistical analyses.

Results: Both CRFA and MRFA provided significant reduction (41 mm and 39 mm, respectively) of chronic knee pain at 24-week. At the 52-week visit, reduction in pain level was sustained for CRFA (42 mm) but seems to decrease for MRFA (31 mm). Improvements in functionality were also significant and sustained with both treatments, although tend to decrease with MRFA at 52-week. Most patients also perceived a very good/good effect of treatments along the duration of the study.

Conclusion: RFA of knee genicular nerves for the treatment of OA chronic pain is effective for 52 weeks post-ablation when using a CRFA (4 mm/17G active tip) or MRFA (10 mm/16G active tip). The benefits of CRFA seems to be better sustained beyond 24 weeks than the ones of MRFA, although no significant differences were observed at 52 weeks.

1. Introduction

Osteoarthritis (OA) is a condition that affects roughly 1 in 7 American adults [1–3]. Incidence of OA is likely to increase as life expectancy is on the rise. The most common cause of joint chronic pain is OA of the knee, due in large part to the knee's major role in weight bearing which is

* Corresponding author. Clinical Research, Lumbrera Research, 33 Derby Way, Bloomington, IL, 61704, USA.
E-mail address: dclumbrera@gmail.com (D.L. Cedeño).

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Table 1
Key eligibility criteria.

Inclusion	Exclusion
• Adult subjects (older than 18 years) • Chronic knee pain (≥6 months) • Radiologic evidence of knee OA (Grade 2–4 Kellgreen-Lawrence) • ≥50 mm VAS for knee pain • Stable regime of pain medication • Positive diagnostic block (≥50% improvement)	• Previous total knee replacement • Connective tissue disease • BMI >40 kg/m^2 • Radicular pain of the affected limb • Active implanted devices • Pregnancy • Uncontrolled conditions, such as diabetes, hypertension, and pulmonary disease • Opioid medication ≥90 mg morphine equivalent

aggravated in overweight patients [4]. Conventional therapies for knee OA pain include physical therapy, analgesics and anti-inflammatory medications, intra-articular injections, and for patients with persistent late-stage symptoms, total knee arthroplasty [5–12]. Many of these interventions are used in patients who are not candidates for surgery, although these may only provide short-term pain relief and are not exempt of significant adverse events. Given the increasing age of the US population, upward trends in obesity prevalence, and lack of satisfactory interventions, the need to find alternative treatments for chronic pain due to knee OA are becoming increasingly critical [4].

Radiofrequency ablation (RFA) of sensory branches of genicular nerves of the knee uses electrical current capable of ablating the tissue near the nerves that innervate structures that are the source of the patient's pain. In 2011, Choi et al. reported that monopolar radiofrequency ablation (MRFA) provided at least 50% knee pain relief in 59% of treated subjects at 12 weeks, when compared to none with a sham treatment [13]. Within RFA therapy, there is a wide range of modalities that may be used in addition to MRFA, including cooled RFA (CRFA). When targeting a particular structure, it is important to consider that the size of a lesion is influenced by several variables beyond relevant anatomical considerations. These include the temperature applied, the duration of the applied current, and the diameter and length of the active tip of the RFA cannula. A larger active tip should generate a larger lesion, and therefore, may provide higher chances to ablate the target nerve [14]. A key difference between CRFA and MRFA is that CRFA involves the use of a 17-gauge probe that allows the introduction of a water-cooling system within the active tip that ablates the target tissue. This cooling effect increases the ablation volume by preventing charring of the tissue immediately around the probe which is thought to allow greater expansion of heat resulting in a larger lesion volume [15,16]. This is a desirable effect because it increases the probability of ablating the target nerve, which often is small, difficult to visualize, and may vary widely in anatomical location from patient to patient. Two randomized control trials (RCT) reported superior outcomes using CRFA over intra-articular corticoid or hyaluronic acid injections [17–19]. A recent RCT implied long-term benefits of CRFA over MRFA (10 mm/18G active tip) although pain relief outcomes were not significantly different at the last 6-month follow up visit of the study [20].

Despite its demonstrated benefit, the high cost of the CRFA system may prevent its routine application when compared to MRFA. For this reason, we set up what we believe to be, the first ever double-blind prospective randomized control trial to compare the efficacy of CRFA and MRFA using an active tip with a comparable diameter (16G) in the treatment of chronic pain due to knee OA. Based on ex vivo measurements, we hypothesized that a cooled RF probe will provide superior improvement and longer duration in pain relief when compared to a monopolar probe of similar size, due to the significantly larger ablation volumes observed with the cooled RF probe [16].

2. Materials and methods

2.1. Study approval and registration

Study was approved by the Western IRB (WIRB, Puyallup, WA) and prospectively registered on 9-Oct-2014 in clinicaltrials.gov (NCT02260869). All subjects enrolled in the study provided informed consent based on voluntary agreement after a thorough explanation of the investigation prior to their participation. Enrollment spanned from 27-Jan-2015 to 17-Apr-2018. Primary endpoint was completed on 15-Oct-2018. All study subjects were enrolled at three different locations affiliated to a private pain center in the Midwest USA. Procedures were performed by interventional pain physicians with at least 5 years of postgraduate experience.

2.2. Study subjects

Potential study subjects were initially identified for the study if they presented with persistent chronic unilateral or bilateral knee pain for at least 6 months despite use of conservative treatment (physical therapy, oral analgesic, steroid injections). Further eligibility criteria are listed in Table 1. Subjects that presented with either one of the exclusion criteria listed in Table 1, were not enrolled for randomization. Prior to

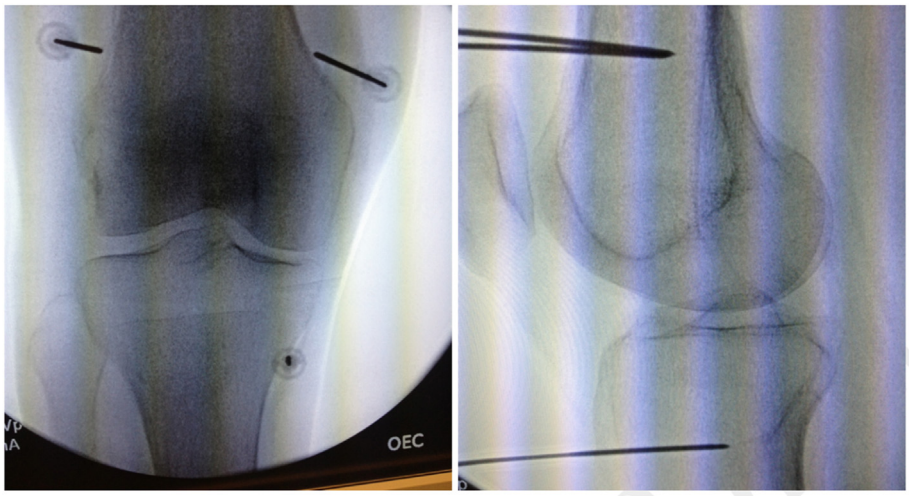

Fig. 1. Representative fluoroscopic x-ray images of the locations of introducing needles previous to RF ablation of the genicular nerves of the knee. Left: AP view; Right: Lateral view.

Table 2
Baseline demographics.

	CRFA	MRFA	P-value (difference between groups)
Sex (n/N (%))			
Female	27/38 (71.1)	25/37 (67.6)	0.939[b]
Male	11/38 (28.9)	12/37 (32.4)	
Age at Consent (years)			
N (subjects)	38	37	
Mean (SD)	62.2 (10.3)	56.8 (12.3)	0.042[a]
BMI (kg/m^2)			
Mean (SD)	33.0 (5.2)	31.9 (4.6)	0.319[a]
Knee Treated (n/N (%))			
Right only	13/38 (34.21)	14/37 (37.84)	
Left only	14/38 (36.84)	13/37 (35.13)	0.947[b]
Bilateral	11/38 (28.95)	10/37 (27.03)	
OA K-L Grade per knee (n/N (%))			
2	30/49 (61.22)	25/47 (53.19)	
3	18/49 (36.73)	19/47 (40.43)	0.487[b]
4	1/49 (2.04)	3/47 (6.38)	
Knee Pain (VAS, mm) – All knees			
N	49	47	
Mean (SD)	74.4 (12.2)	73.0 (11.3)	0.558[a]
Knee Pain (VAS, mm) – Unilateral knees			
N	27	27	
Mean (SD)	71.6 (12.1)	73.5 (11.3)	0.541[a]
Knee Pain (VAS, mm) – Bilateral knees			
N	22	20	
Mean (SD)	77.9 (11.6)	72.3 (11.4)	0.123[a]

[a] T-test for independent means.
[b] Chi-square test for proportions.

enrollment, potential subjects had undergone a single fluoroscopically guided diagnostic block. Those reporting over 50% pain reduction from the block were considered for informed consent and enrollment.

Enrolled subjects were block randomized 1:1 into either CRFA or MRFA using stratification by sex and whether unilateral or bilateral knee OA. Sealed envelopes with a binary identification marker for treatments (A or B) were presented to patients by a blinded investigator. If a patient presented with bilateral osteoarthritis, both knees were treated using the same treatment as per randomization, and data was recorded for each knee independently. Although prevalence of patients with bilateral knee OA is likely to be larger than that of patients with unilateral [21], the number of patients with bilateral knee OA in the study was limited to 15 per treatment group. Given that perception of pain intensity and function seems to differ between populations with unilateral and bilateral knee osteoarthritis, the group of patients with the bilateral condition was considered a subgroup during the analysis of the data.

Patients and research staff in charge of the evaluation of treatments were blinded to the treatment assignment. Due to the evident intrinsic hardware differences between cooled and monopolar RF ablation systems it was not possible to blind the pain physicians and clinical staff present during the procedure. Details on the hardware and procedure were concealed from the patient in the operating room. The interventional pain physician involved during the RF procedure was excluded from the subjects follow up visits during the duration of the study.

2.3. Study design

This was a prospective, double-blind, single center randomized control trial designed to compare CRFA to MRFA of the geniculate nerves in the treatment of chronic OA knee pain. Enrolled eligible subjects were randomized into either treatment group using randomization envelopes. Procedures were done on day 0 of the study, with follow ups occurring 1 week (±3 days), 4 weeks (±1 week), 12 weeks (±2 weeks), 24 weeks (±2 weeks), and 52 weeks (±2 weeks) post-procedure.

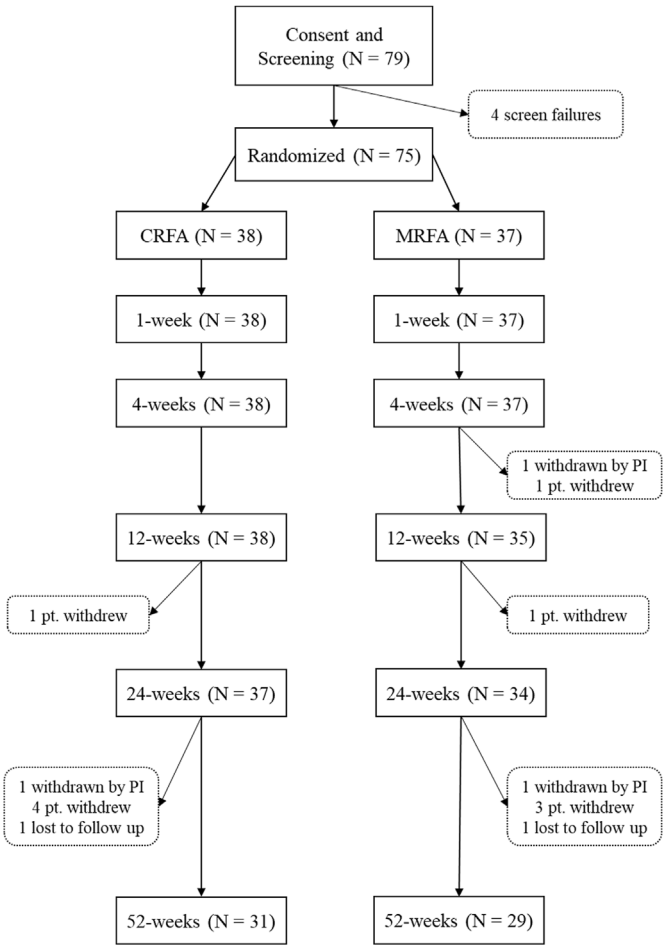

Fig. 2. Flow of subject disposition throughout the study follow up. There were 5 subjects in CRFA group and 7 subjects in MRFA group that withdrew consent or were withdrawn by investigator due to lack of pain relief and pursuing of other treatments.

2.4. Diagnostic blocks

Subjects underwent fluoroscopically guided single diagnostic blocks of the geniculate nerves (superior medial, superior lateral, and inferior medial) with 0.5 mL of local anesthetic (1% Lidocaine). They were eligible for enrollment following a positive response, which was defined as ≥50% pain relief. Patients presenting with bilateral knee pain were subjected to a separate diagnostic block for each knee.

2.5. Treatments

Under sterile conditions, patients were placed in supine position on a fluoroscopic table with a pillow under the popliteal fossa. Then an anterior-posterior (AP) fluoroscopic view of the tibio-femoral joint was obtained. Skin and subcutaneous tissues were anesthetized using Lidocaine 1% before placing the RFA introducers, which were advanced percutaneously towards the junction of the shaft with the epicondyle until bone contact was made. Then the introducer was displaced laterally a couple of mm away from the bone. This process was performed at the superior medial, and superior lateral aspects of the femur as well as the inferior medial aspect of the tibia. Then the fluoroscope was rotated to obtain a lateral view to guide the depth of the needle to be at the medial third of the femur or tibia. At this point, the stylet of the introducer was

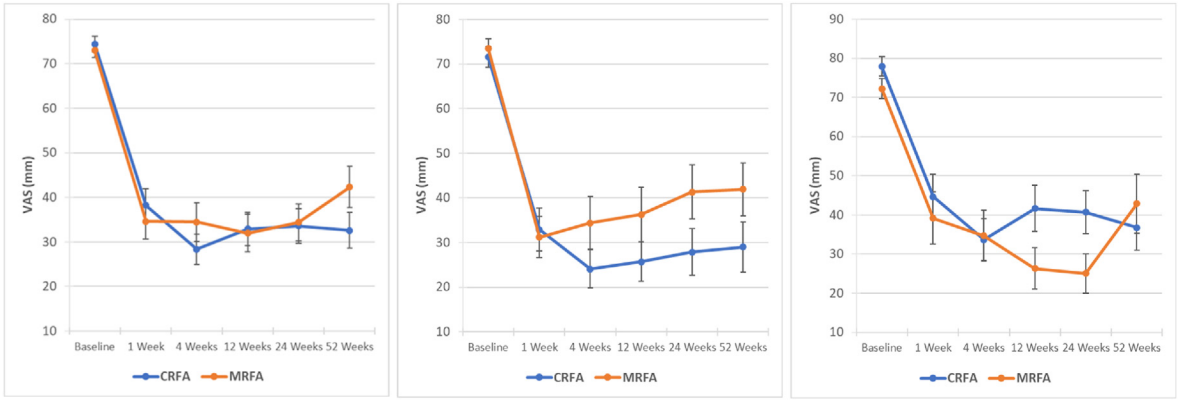

Fig. 3. Left panel: Mean VAS scores including all subjects combined. Sample sizes are 49 knees for CRFA and 47 knees for MRFA and correspond to the ITT population. Center panel: Mean VAS scores in subjects with unilateral knee pain (27 knees treated with either CRFA or MRFA). Right panel: Mean VAS scores in subjects with bilateral knee pain (22 knees treated with CRFA and 20 treated with MRFA). Bars are standard errors. All improvements from baseline are significant ($p < 0.001$).

Table 3
Changes in VAS scores relative to baseline at different evaluation time points.

PAIN RELIEF				
Change VAS (mm) - ALL	4-week	12-week	24-week	52-week
CRFA (N = 49)	−46.0 ± 3.4	−41.5 ± 3.7	−40.7 ± 3.8	−41.9 ± 4.3
MRFA (N = 47)	−38.4 ± 4.0	−40.9 ± 4.2	−38.6 ± 4.1	−30.7 ± 4.6
Change VAS (mm) - Unilateral				
CRFA (N = 27)	−47.4 ± 4.3	−45.8 ± 5.0	−43.7 ± 5.6	−42.5 ± 6.4
MRFA (N = 27)	−39.1 ± 5.4	−37.3 ± 6.4	−32.2 ± 6.0	−31.6 ± 5.8
Change VAS (mm) - Bilateral				
CRFA (N = 22)	−44.2 ± 5.5	−36.2 ± 5.3	−37.1 ± 5.1	−41.1 ± 5.8
MRFA (N = 20)	−37.6 ± 6.1	−45.9 ± 4.9	−47.2 ± 4.4	−29.4 ± 7.8

Mean ± SEM. All changes in VAS relative to baseline were significant ($p < 0.001$).

removed, and the RF probe was advanced through the introducer. Fig. 1 shows representative x-ray images of the placement of the needles. A grounding pad was placed in a distal skin surface of the patient's body. Sensory and motor stimulation were assessed previous to ablation using a commercially available RFA generator (PMG115-TD V4.0, Kimberly Clark, Roswell, GA, USA). RFA was started upon verification of appropriate impedance measurements (typically below 150 Ω). CRFA treatment was provided using commercial probes with 4 mm active tip and 17G diameter (CRK-17-100-4, Halyard Health, Alpharetta, GA, USA). Immediately before the beginning of the ablation, 0.5 mL of Lidocaine 1% in isotonic saline were injected at each site. RFA was applied within 30 s of the injectate. CRFA treatment was applied for 150 s at 80 °C ablation temperature, which corresponds to a 60 °C cooled tip temperature. MRFA treatment was provided using a commercial RFA probe (PMP-20-100C-SU, Halyard Health, Alpharetta, GA, USA) inserted into a corresponding RFA cannula with a 10 mm active tip and 16G diameter (RF Sharp Needle 233–1610, Epimed, Dallas, TX, USA). MRFA treatment was applied for 90 s at 80 °C ablation temperature.

At the investigator discretion patients were allowed to continue their usual standard of care. No increase in opioid medication was allowed throughout the study execution. Analgesics could be used to mitigate post-procedural pain and pain due to AEs. However, the use of additional analgesics was to be stopped at least two weeks before a follow up study visit.

2.6. Study outcomes

The primary endpoint of the study was mean change from baseline knee pain as measured by a visual analogue scale (0–100 mm VAS) at 24 weeks post-RFA with success defined as a reduction in mean VAS of at least 20 mm. Secondary endpoints include changes at 1, 4, 12 and 52 weeks for pain scores (VAS), the Western Ontario and McMaster University Osteoarthritis (WOMAC) index, the Oxford Knee Score (OKS), and a Global Perceived Effect questionnaire (5-point Likert scale).

Each subject was evaluated for adverse events (AEs) at every visit. AEs were any unfavorable, unintended sign, symptom, or disease whether or not considered related to the treatment. AEs were categorized as mild, moderate, or severe and were considered serious when were life threatening or fatal; permanently incapacitated or disabled a subject; or required in-patient hospitalization longer than 24 h.

2.7. Data analysis

Data analysis was based on the intention to treat population (ITT) using available data from subjects at any given evaluation time point. Missing data was imputed by carrying out the last observation forward (LOCF). For bilateral subjects, each knee was evaluated separately, thus the number of available data (i.e., knees evaluated) was doubled in these cases.

The primary outcome analysis was based on the reduction of pain scores (VAS) between each treatment group and baseline at 24 weeks post-treatment. Reduction in VAS scores at 1, 4, 12, and 52 weeks for each treatment and baseline were also determined, and their difference evaluated in the same manner for 24 weeks. The difference in pain reduction (relative to baseline) between CRFA and MFA was also evaluated at all time points. A sample size calculation indicated that 44 subjects allocated in each group would have 80% power to detect a difference in means of 15 mm in VAS scores between treatments assuming a common standard deviation of 25.4 mm using a one-way ANOVA approach with a 5% two-sided significance level.

Additional continuous outcomes such as OKS and WOMAC index were also compared for every treatment relative to basement and among each other at every evaluation time point. Significance for continuous variables was calculated using a two-sided independent t-tests, or Mann-Whitney rank sum test if the data did not appear sufficiently normally distributed, with a significance level $\alpha = 0.05$. Categorical outcomes were evaluated using a Chi square test for proportions at a significance level $\alpha = 0.05$. Values of $p < 0.05$ indicated a significance difference between comparisons. Analyses were also done for the subsets of subjects that received unilateral and bilateral treatment.

Table 4
Assessment of knee functionality at different evaluation time points.

KNEE FUNCTIONALITY (Oxford Knee Score)					
OKS - ALL	Baseline	4-week	12-week	24-week	52-week
CRFA (N = 49)	19.9 ± 1.1	31.6 ± 1.1	30.6 ± 1.3	30.6 ± 1.4	31.9 ± 1.5
MRFA (N = 47)	17.7 ± 0.8	30.6 ± 1.4	30.9 ± 1.6	30.4 ± 1.6	27.5 ± 1.7
OKS - Unilateral					
CRFA (N = 27)	20.3 ± 1.3	32.3 ± 1.4	31.9 ± 1.7	31.9 ± 2.1	32.7 ± 2.0*
MRFA (N = 27)	17.4 ± 1.0	30.7 ± 1.9	29.9 ± 2.3	27.3 ± 2.1	26.0 ± 2.3
OKS - Bilateral					
CRFA (N = 22)	19.5 ± 1.8	30.9 ± 1.8	29.1 ± 2.0	29.0 ± 1.8	31.0 ± 2.2
MRFA (N = 20)	18.1 ± 1.3	30.5 ± 2.2	32.2 ± 2.2	34.6 ± 2.4	29.5 ± 2.5
KNEE FUNCTIONALITY (WOMAC Components)					
WOMAC Physical - ALL	**Baseline**	**4-week**	**12-week**	**24-week**	**52-week**
CRFA (N = 49)	40.3 ± 1.7	22.9 ± 1.9	21.2 ± 1.9	24.7 ± 2.2	21.6 ± 2.1
MRFA (N = 47)	43.1 ± 1.1	23.2 ± 2.1	23.9 ± 2.5	22.9 ± 2.4	27.2 ± 2.4
WOMAC Physical - Unilateral					
CRFA (N = 27)	37.4 ± 2.1	19.7 ± 2.2	18.6 ± 2.5	22.1 ± 3.5	20.2 ± 2.8
MRFA (N = 27)	43.1 ± 1.4	21.9 ± 2.9	24.6 ± 3.6	27.7 ± 3.2	27.1 ± 3.3
WOMAC Physical - Bilateral					
CRFA (N = 22)	43.8 ± 2.5	26.7 ± 2.9	24.4 ± 2.7	27.9 ± 2.3*	23.4 ± 3.1
MRFA (N = 20)	43.1 ± 1.7	25.1 ± 3.1	23.0 ± 3.3	16.4 ± 3.0	27.4 ± 3.5
WOMAC Pain - ALL					
CRFA (N = 49)	11.7 ± 0.4	6.5 ± 0.5	6.1 ± 0.5	7.2 ± 0.6	5.9 ± 0.6
MRFA (N = 47)	12.4 ± 0.4	6.6 ± 0.6	7.0 ± 0.7	6.6 ± 0.7	7.6 ± 0.7
WOMAC Pain - Unilateral					
CRFA (N = 27)	10.9 ± 0.5	5.4 ± 0.6	5.4 ± 0.6	6.3 ± 1.0	5.4 ± 0.8
MRFA (N = 27)	12.2 ± 0.4	6.4 ± 0.8	7.1 ± 1.0	8.2 ± 0.9	7.9 ± 1.0
WOMAC Pain - Bilateral					
CRFA (N = 22)	12.7 ± 0.7	7.7 ± 0.9	7.0 ± 0.9	8.3 ± 0.7*	6.5 ± 1.0
MRFA (N = 20)	12.6 ± 0.6	6.8 ± 1.0	6.8 ± 0.9	4.4 ± 1.0	7.3 ± 1.0
WOMAC Stiffness - ALL					
CRFA (N = 49)	4.9 ± 0.2	3.0 ± 0.2	2.7 ± 0.3	3.1 ± 0.3	3.0 ± 0.3
MRFA (N = 47)	5.3 ± 0.3	2.7 ± 0.3	2.7 ± 0.3	2.7 ± 0.3	3.3 ± 0.3
WOMAC Stiffness - Unilateral					
CRFA (N = 27)	4.7 ± 0.3	2.9 ± 0.3	2.5 ± 0.3	2.9 ± 0.4	3.0 ± 0.4
MRFA (N = 27)	5.1 ± 0.3	2.7 ± 0.4	2.7 ± 0.4	3.5 ± 0.4	3.2 ± 0.3
WOMAC Stiffness - Bilateral					
CRFA (N = 22)	5.3 ± 0.4	3.2 ± 0.4	3.0 ± 0.5	3.3 ± 0.4*	3.1 ± 0.4
MRFA (N = 20)	5.7 ± 0.4	2.9 ± 0.4	2.8 ± 0.4	1.7 ± 0.4	3.4 ± 0.4

Mean ± SEM. All increases in OKS relative to baseline and decreases in a WOMAC component relative to baseline were significant ($p < 0.001$). * denotes $p < 0.05$ for CRFA vs MRFA comparison at a given timepoint.

3. Results

3.1. Subject profile

Table 2 summarizes the baseline demographics of the study. A total of 79 subjects consented participation in the study, with 75 of them being eligible under the study criteria for randomization. These subjects were distributed randomly into the CRFA and MRFA groups. Fig. 2 shows the subject disposition throughout the study duration. Due to the stratification by sex and laterality of knee treated, there were no significant differences expected and indeed p values for these categories were above 0.9. Interestingly, there was significant difference ($p = 0.042$) in the mean age of the subjects enrolled in each group, with the population in the CRFA group being older by about 5 years. Mean BMI in the study was above 30 kg/m^2 implying that most patients were overweight or obese. More than 90% of the knees studied presented grade 2 or 3 OA according to the radiologically based Kellgren-Lawrence scale.

3.2. Knee pain relief

Fig. 3 shows VAS scores for each evaluation time point, while Table 3 shows the corresponding mean changes in VAS relative to baseline. In all cases, improvement (reduction of VAS) is significantly different ($p < 0.001$) from baseline for both treatments. The reduction was >20 mm, which is sustained throughout the 52 weeks follow up. Therefore, primary endpoint of the study was successful. There were not significant differences between the two RFA treatments at any time point.

The study allowed for treatment of subjects with unilateral and bilateral knee pain. A subgroup analysis indicates a trend for better results with the CRFA in unilateral cases than bilateral cases, with an additional reduction of VAS between 11 and 12 mm in the 24 and 52 weeks. Fig. 3 and Table 3 show mean VAS scores and changes in VAS. Improvements were significant relative to baseline score in both cases.

3.3. Improvements in functionality

Table 4 lists mean Oxford knee scores (OKS) for each evaluation time point. The OKS ranges from 0 to 48, with a score of 48 being the best possible outcome. There is a significant improvement (i.e., increase in OKS) for all mean OKS at every time point relative to baseline scores, except at 1 week follow up. There are not significant differences in mean OKS between treatments, although at the 52 weeks follow up, the score for CRFA (31.9 ± 10.4) tends to be larger ($p = 0.050$) relative to the score obtained with MRFA (27.5 ± 11.6). The substantial improvement in OKS provided by CRFA is significant relative to MRFA for unilateral cases ($p = 0.034$) at 12 months. The improvement in OKS obtained with CRFA is sustained, while OKS in subjects treated with MRFA starts to decline at the 24 weeks follow up.

Table 4 also lists the WOMAC's categories for all subjects as well as for subjects with unilateral knee pain and subjects with bilateral pain separately. All improvements (i.e., decrease in WOMAC scores) relative to baseline are significant for both treatments throughout the various time points. There are not significant differences between treatments. Differences in means between treatments at the different time points are not significant, except for bilateral cases at 24 weeks.

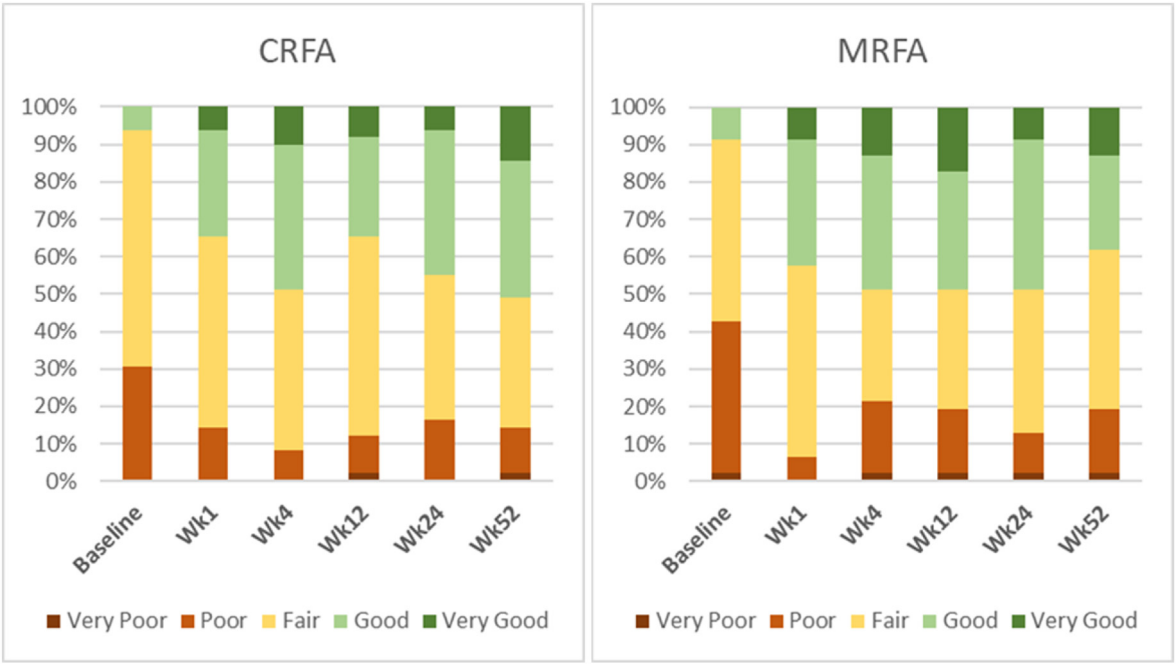

Fig. 4. Global perceived effect for all subjects from baseline to 52 weeks visit. Sample sizes are 49 knees for CRFA and 47 knees for MRFA and correspond to the ITT population. Unilateral sample sizes are 27 knees for CRFA and 27 knees for MRFA. Bilateral sample sizes are 22 knees for CRFA and 20 knees for MRFA. These sizes correspond to the ITT population.

3.4. Global perceived effect

Fig. 4 shows bar graphs with results of the global perceived effect (GPE) of subjects in both treatment arms when asked the question: "Considering all the ways your osteoarthritis in your knee affects you, how are you doing today". There was a notable improvement in the GPE as a result of RF treatment, even as early as 1 week after the procedure. Perception was sustained and even improved over time with 45% and 51% of subjects in the CRFA arm experiencing a very good/good effect at 24 and 52 weeks, while 49% and 38% subjects in the MRFA arm experienced a very good/good effect at the same time points. This highly differs from the 6–8% of subjects that reported a good experience at baseline. The GPE for unilateral and bilateral subjects, illustrated in Fig. 5, shows similar results and trends.

3.5. Adverse events

Table 5 summarizes all reported AEs. A total of 70 AEs were reported in 37 subjects. However, only 3 of these AEs in 3 subjects were deemed definitively (1), probably (1) or possibly (1) related to RFA treatments. Treatment in these cases resulted in moderate worsening of knee pain, which required adjustment of pain analgesics in two cases to be resolved. There were 6 serious AEs in 4 subjects, all of these AEs were unrelated to the treatments. No deaths were reported.

4. Discussion

The treatment of chronic knee pain due to OA using MRFA or CRFA has been shown to be effective and sustainable [17–20,22–26]. Although the effectiveness of CRFA has been demonstrated to be better than standard intraarticular treatments [17–19,25], only one prospective comparative clinical study between MRFA and CRFA has been recently reported [20] in which a 10 mm/18G active tip was used for MRFA. Although utilization of 18G or 20G needles in MRFA is traditionally used, preclinical work by Cedeño et al. [16] implied that lesions obtained with a 10 mm/16G active tip would produce lesion volumes that may be comparable with those produced by a standard CRFA probe (4 mm/17G active tip).

Our results indicate that both MRFA and CRFA treatments used under the conditions in this study provide significant knee pain relief that is sustained for 52 weeks. There were not significant differences between mean values for improvements in pain levels for both treatments. Reduction in VAS scores from baseline with CRFA in the present study at the 24-week primary endpoint is comparable to results reported by Davis et al. (reduction range 4.2–4.9 points on the 0–10 NRS scale) [19,25]. The % reduction from baseline due to CRFA in our study (55–62%) is slightly below the 58–67% reported by Davis et al. [23] and the 57–67% reported by Chen et al. [17,18], and larger than the 33–41% reported by Vanneste et al. [20]. A procedural difference in the latest study is that a diagnostic nerve block was not performed. Using a diagnostic nerve block may improve patient selection and better RFA outcomes. Also, these authors included patients with persistent pain after total knee replacement, which may respond different to RFA treatment. The % reduction from baseline due to MRFA with a 10 mm/16G in our study (46–56%) is larger than the 19–29% range reported by Vanneste et al. for MRFA with a 10 mm/18G active tip. This suggests that using a larger diameter (16G) would provide better results, consistent with the expected benefit of producing a larger lesion volume with the thickest active tip. Results of our study are also consistent with those reported by Kapural et al. [26] in a retrospective study that compared the efficacy of CRFA with MRFA. Although clinicians in that study mostly used 22G and 18G active tips, the mean VAS scores for the first 4–6 weeks for CRFA and MRFA were comparable when a 16G active tip was used. Furthermore, the study by Kapural et al. found that the efficacy of CRFA is sustained for a longer period than when using MRFA, particularly when small diameter needles were used.

Both CRFA and MRFA provided significant improvements in patient functionality as demonstrated by the changes in OKS and WOMAC categories. Treatments provided improvements in OKS ranging between 11 and 12 points with CRFA and 10–13 points with MRFA. This improvement is a clinically meaningful change based on other type of intervention [27]. This translates into sustained improvement from moderate to severe joint function at baseline to mild joint function after 4 weeks of treatment. Similarly, CRFA and MRFA produced significant

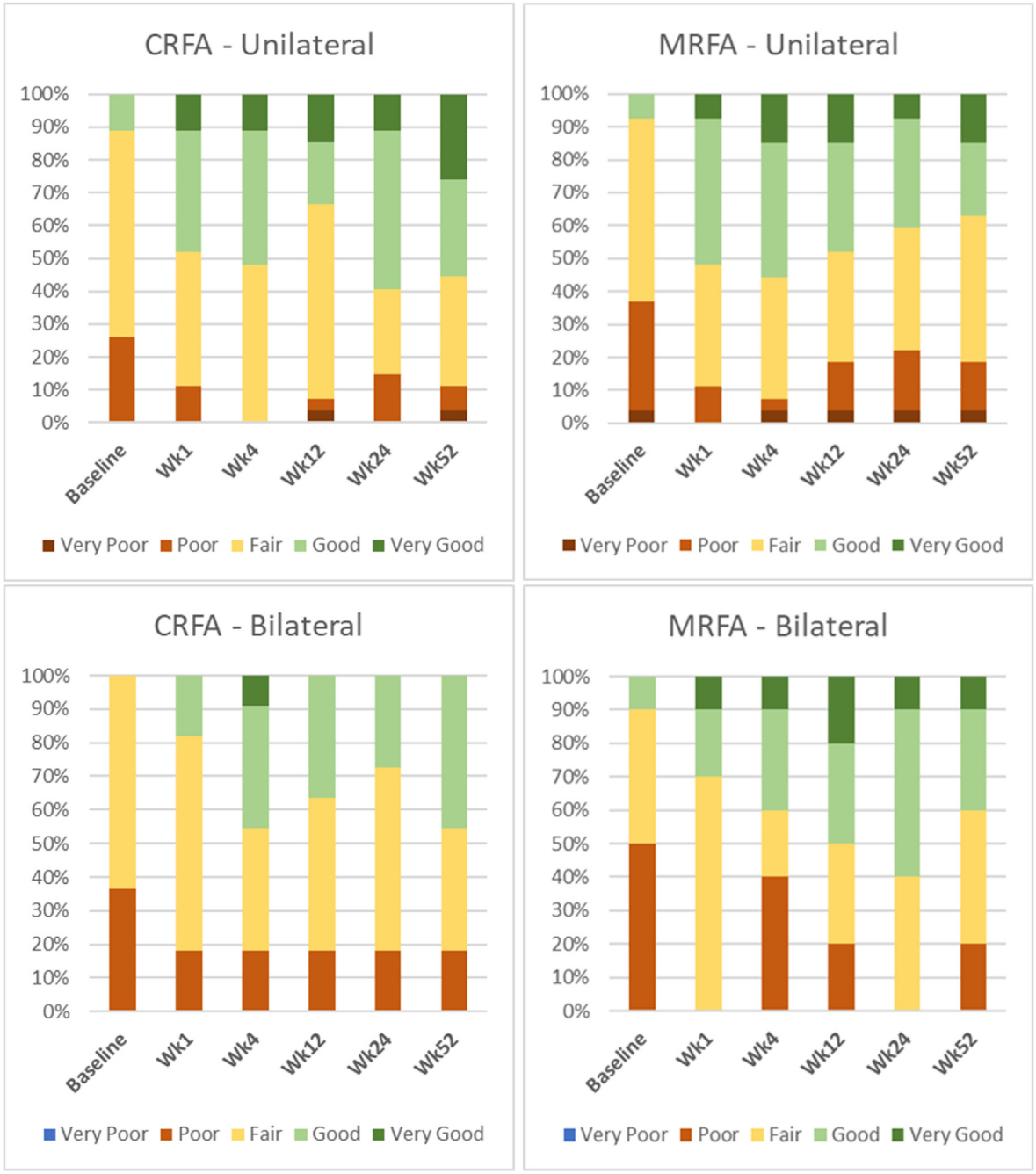

Fig. 5. Global perceived effect from baseline to 52 weeks visit for unilateral (top panels) and bilateral (bottom panels) subjects.

improvements in the three components of the WOMAC. The improvements represent about 25% in the physical scale (0–68 points), pain scale (0–20 points) and stiffness scale (0–8 points), which are above what is considered clinically important changes with other treatments, including total knee arthroplasty [28,29]. The total WOMAC scores (sum of components) are comparable to those previously reported by Chen et al. [17], except that WOMAC baseline was about 10 points lower in our study.

Patients perceived that treatment provided a global benefit. About 50% of patients in both treatment arms reported feeling good and very good after 24 weeks of treatment. This is a notable difference from the 7% of patients that felt the same way at baseline. Although there were not significant differences between treatments along the study duration, it is interesting to note a decline in the very good/good responders with MRFA treatment at 52 weeks which contrasts with an increase in subjects treated with CRFA.

In order to provide a study population representative of the general population, our study included subjects with both unilateral (N = 27 in each group) and bilateral (N = 11 in CRFA, 10 in MRFA) knee pain. Although outcomes in subjects with bilateral pain treated with CRFA or MRFA seem different than for those subjects with unilateral pain, these were not significant. Mean reduction in pain level relative to baseline with CRFA and MRFA reflect a significant benefit for both of the population subsets. In general, improvements in functionality (WOMAC indexes and OKS) also reflected the trends in VAS reduction over time and the benefits of CRFA and MRFA treatments. The reported global perceived effect also reflects improvements in both subsets and no significant differences in CRFA and MRFA treatments in the long term.

The number of adverse events related to treatments or procedures was low (3 events in 75 patients). All of them were classified as increased pain post-procedure, which was anticipated. There were 6 serious adverse

Table 5
Summary of adverse events.

	CRFA N = 38 subjects		MRFA N = 37 subjects	
	Events n	Subjects n (%)[b]	Events n	Subjects n (%)[b]
Relationship to Procedure/Treatment				
Related				
Increased knee pain	1	1 (2.6)	2	2 (5.4)
Not Related	38	18 (47.4)	32	19 (51.3)
Severity				
Serious[a]	2	2 (5.3)	4	2 (5.4)
Moderate	34	15 (39.5)	25	15 (40.5)
Mild	3	3 (7.9)	5	5 (13.5)

[a] None related to study: Two in CRFA group were: pneumonia, and broken bone; Four in MRFA group were: pneumonia, worsening of reflux esophagitis, hypokalemia, and acute kidney injury.
[b] Relative to total number of subjects in group (i.e., ITT population).

events, although none of them related to treatments or procedures. These events occurred in 4 patients, with three of them occurring in one patient.

The study was successful in demonstrating that both CRFA (4 mm/17G active tip) and MRFA (10 mm/16G active tip) of three genicular nerves of the knee provide significant and sustained pain relief and improvements in functionality up to 52 weeks post treatment. A limitation of the study is that it was not powerful enough to determine if the observed differences in mean pain reduction from baseline between CRFA and MRFA were statistically significant. Unfortunately, due to financial constraints, the study was terminated by the sponsor before reaching the originally intended sample size of at least 88 randomized subjects in each group, but the current results implies that the differences between CRFA and MRFA are not clinically significant. Although including patients with bilateral subjects in the study was well intended, this was a confounding factor which was clearly another limitation of the study. Another limitation is that the study was performed in a single research center although in three separate locations. It is plausible that bias was introduced by the impossibility of blinding the treatment allocation to the physician investigators in charge of the procedure. This bias was minimized by preventing them from interacting with subjects they treated for the rest of the study. Other research staff as well as patients were fully blinded to treatment allocations throughout the length of the study. Another limitation refers to the difference in the duration of the procedure in the MRFA (90 s) versus the CRFA (150 s). In order to maintain with standard practice in many clinics at the time of the execution of the study, the most common device settings for ablation times and temperatures were used. Although MRFA is conventionally applied for 90 s, Provenzano et al. [30] demonstrated that the ablation surface area increases with time, with the maximum lesion occurring at 180 s. It is conceivable that by extending the duration of the MRFA treatment, a larger lesion in the MRFA group could have extended the duration of the effects in this group. Our study may also be limited because it only targeted RFA of three genicular nerves. Recent discussions in the field [31,32] suggest that RFA of additional targets should provide better outcomes, due to the large anatomical variability of knee sensory innervations. Interestingly, results by Chen et al. [17,18] using CRFA on 4 targets and those of Davis et al. [19,24] using CRFA on 3 targets (as used herein) yielded similar results.

5. Conclusion

Our study demonstrated that CRFA or MRFA (using an active tip of comparable diameter) of geniculate nerves provide significant long-lasting improvements in pain and function for those patients suffering with chronic knee OA. Our study did not demonstrate statistical differences between the two groups, and the differences were not considered clinically significant. Considering the benefits of both therapies, clinicians may want to balance the potential longer lasting benefits of both treatments used in this study versus the cost of the technologies during their decision-making process.

Trial registration

Registered in clinicaltrials.gov, NCT02260869. https://clinicaltrials.gov/ct2/show/NCT02260869.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ricardo Vallejo reports financial support was provided by Kimberly-Clark Corporation. David L. Cedeno and Ricardo Vallejo report a relationship with Medtronic Inc that includes: consulting or advisory.

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