KJP

Korean J Pain 2024;37(1):13-25
https://doi.org/10.3344/kjp.23344
pISSN 2005-9159, eISSN 2093-0569

Review Article

Cooled radiofrequency ablation of genicular nerves for knee osteoarthritis

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ABSTRACT

Knee osteoarthritis (OA) is a prevalent and debilitating musculoskeletal condition that significantly affects the quality of life of millions of individuals worldwide. In recent years, cooled radiofrequency ablation (CRFA) has become a viable treatment option for knee OA. This review thoroughly evaluated the existing literature on CRFA therapy for knee OA. It delved into the mechanisms behind CRFA, evaluated its clinical efficacy, and investigated potential avenues for future research and application. The insights gained from this review are crucial for healthcare professionals, researchers, and policymakers, offering an updated perspective on CRFA's role as a viable therapeutic option for knee OA.

Keywords: Chronic Pain; Cooled Radiofrequency Ablation; Denervation; Hyaluronic Acid; Injections, Intra-Articular; Osteoarthritis, Knee; Radiofrequency Ablation; Steroids; Treatment Outcome.

INTRODUCTION

Knee pain is a common issue in adults, with a steadily increasing prevalence [1,2]. There are many causes of knee pain, such as meniscal and tendon injuries, posttraumatic syndrome, and postsurgical pain; osteoarthritis (OA) is the leading cause [3]. Risk factors for developing knee OA include obesity, previous knee trauma, muscle weakness, diabetes, and age-related degenerative changes [3]. Knee OA is a pervasive and debilitating musculoskeletal condition affecting millions of individuals worldwide [4]. Characterized by the progressive degeneration of the articular cartilage, knee OA poses a significant challenge to both patients and healthcare providers. Although traditional treatment modalities, including analgesics, physical therapy, and intra-articular steroid (IAS) injections, have long been employed to manage symptoms, the growing need for more effective and minimally invasive interventions has prompted the exploration of novel approaches [5]. Among these newer treatments, genicular nerve (GN) radiofrequency ablation (RFA) has emerged as a viable alternative to conservative therapy and total knee arthro-

Received December 7, 2023; Revised December 16, 2023; Accepted December 18, 2023

Handling Editor: Francis S. Nahm

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plasty [6].

Thermal RFA was first described in 1960 and later applied to the spinal facet joints in the 1970s as a method to alleviate back pain [7,8]. This method ablates nerves by raising the local tissue temperatures to approximately 80°C–90°C with radiofrequency probes [9]. In contrast, pulsed RFA, introduced in 1998, is an ablation technique that does not destroy tissues. Pulsed RFA is achieved by alternating extended "off" periods that permit heat dissipation with brief, high-voltage current bursts [6]. This intermittent electrical delivery prevents tissue injury, and the target tissue can remain below 42°C [10]. Choi et al. [11] initially suggested RFA for GNs in knee OA treatment in 2010. Before genicular RFA, it is recommended to perform diagnostic blocks with a local anesthetic on the target nerve, which is located outside the knee joint to avoid potential motor nerve damage. Both thermal and pulsed RFA techniques have been employed for GN ablation. RFA is effective for native osteoarthritic knee pain [12] and is being added to knee OA management guidelines as an additional treatment modality [13,14].

In recent years, cooled radiofrequency ablation (CRFA) has emerged as a promising alternative treatment modality for knee OA [15]. Unlike conventional radiofrequency procedures, CRFA utilizes advanced cooling technology to target and modulate the sensory nerves responsible for transmitting pain signals. CRFA offers a larger treatment zone than conventional thermal RFA and increases the chance of encompassing the nerve within the ablation lesion, potentially providing longer-lasting pain relief by conferring a larger isotherm lesion than conventional RFA through the internal infusion of cool water into the needle during the procedure [6].

This review synthesized the existing literature to provide a robust foundation for clinicians, researchers, and policymakers to understand the current status of CRFA in knee OA treatment. The objective of this review was to comprehensively examine the landscape of CRFA in the context of knee OA, including the mechanism of action, anatomy of knee innervation, procedural technique, clinical efficacy, safety profile, and potential advancements.

MAIN BODY

1. Mechanism of action

CRFA has emerged as a novel therapeutic option, particularly due to its unique mechanism of action. To understand the therapeutic potential of CRFA, it is imperative to unravel the intricate mechanism of action that distinguishes CRFA from conventional RFA procedures. The therapeutic mechanism of conventional RFA is based on the idea that it blocks nociceptive pain signals through A-δ and C-fibers from the peripheral nervous system to the central nervous system while preserving motor or sensory (A-β) fibers [16]. Furthermore, the conventional RFA-induced lesions, which can cause localized neuronal tissue destruction and thermocoagulation, have been demonstrated to exhibit scar formation features, such as cell necrosis, fibrosis with collagen fiber deposition, and an acute inflammatory response [17].

1) Neural modulation

The efficacy of RFA lies in its ability to modulate neural pathways responsible for transmitting pain signals from the knee joint to the central nervous system [18]. Unlike conventional RFA, CRFA incorporates advanced cooling technologies, allowing for more targeted and controlled applications of thermal energy [19]. By precisely cooling the electrode during the procedure, CRFA selectively disrupts the function of the sensory nerve fibers without causing extensive thermal damage to the surrounding tissues [18].

2) Temperature-controlled precision

The cooling component of the CRFA is critical for maintaining a temperature-controlled environment during the ablation process [6]. This cooling components involves circulating a cooling medium (such as saline) through the electrodes to prevent excessive heating of the surrounding tissue (**Fig. 1**). This cooling mechanism allows for more controlled and targeted application of radiofrequency energy, which is important to prevent damage to adjacent nerves or structures [20]. Controlled cooling not only enhances the safety profile of CRFA but also enables the creation of larger lesions, optimizing the disruption of aberrant pain signaling pathways [18,21]. Moreover, it has been reported that CRFA results in the formation of spherical lesions with diameters ranging from 12.3 to 12.8 mm [22,23].

3) Lesion formation and nerve impairment

CRFA induces the formation of thermal lesions within the targeted nerves, impairing their ability to effectively transmit pain signals [23]. The cooling mechanism ensures a gradual and controlled temperature increase,

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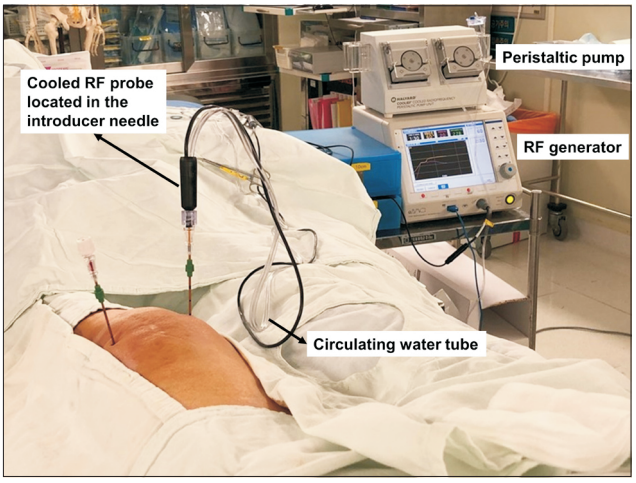

Fig. 1. Cooled radiofrequency (RF) system consists of guide introducers and cooled radiofrequency probe, radiofrequency generator, and peristaltic pump unit.

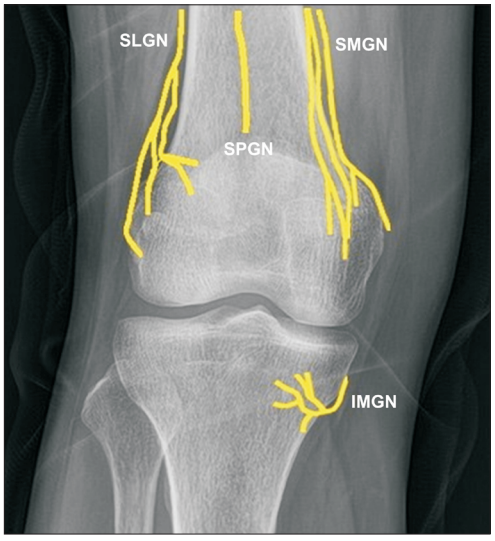

Fig. 2. Schematic daiagram of the right anterior knee joint innervation for genicular nerves interventions. IMGN: inferior medial genicular nerve, SLGN: superior lateral genicular nerve, SMGN: superior medial genicular nerve, SPGN: suprapatellar genicular nerve.

leading to the creation of lesions that are not only precise but also tailored to the specific neural architecture of the knee joint [17]. The targeted lesion disrupts the nociceptive signaling cascade, thereby alleviating pain and improving overall joint function [19,21].

4) Anti-inflammatory effects

In addition to its primary role in neural modulation, CRFA is associated with secondary anti-inflammatory effects. TNF-α secretion was elevated when the radiofrequency was applied to monocytes in tissue culture [24], and gene expression related to immune system modulation, specifically anti-inflammatory genes, was significantly elevated when pulsed radiofrequency was applied to astrocytes [25]. There is evidence from use of radiofrequency that it can reverse oxidative stress associated with immunological functions; this is probably mostly due to the magnetic field component of radiofrequency [26]. This feature of the CRFA mechanism contributes to the attenuation of inflammation in arthritic knees, potentially offering a multifaceted approach to symptom management [17].

2. Anatomy of the GN for CRFA

The knee has highly complex neural innervation. The articular branches of various main nerves, such as the femoral, tibial, common peroneal (fibular), saphenous, and obturator nerves, are known as the GNs and innervate the knee [27,28]. Specifically, the superolateral quadrant of the anterior knee is innervated by the muscular branches of the femoral nerve, superior lateral genicular nerve (SLGN), and common fibular nerve. The superomedial quadrant receives innervation from the muscular branches of the femoral nerve, and superior medial genicular nerve (SMGN). The inferolateral quadrant is innervated by the inferior lateral genicular nerve (ILGN) and the recurrent peroneal nerves, while the inferomedial quadrant is innervated by the inferior medial genicular nerve (IMGN) and infrapatellar branch of the saphenous nerve [29]. While there has been some debate regarding the existence of GNs, the majority of literature supports their presence [29–33]; many variations exist and these are excluded from this review. The GNs are located on the periosteum before entering the knee joint capsule and usually travel with the genicular artery [29]. Consequently, the SMGN, SLGN, and IMGN branches are frequently targeted in procedures because of their proximity to bony landmarks (**Fig. 2**) [11,34]. The ILGN block is usually avoided due to its close proximity to the peroneal nerve [20]. Importantly, interventions for these GNs can mainly reduce anterior knee joint pain, but may not be effective for pain originating in the posterior knee joint [29,35].

3. Patient selection and procedure technique in CRFA for knee OA

A thorough understanding of patient selection criteria

and the intricacy of the procedural technique is important for optimizing outcomes. This section discusses the considerations that guide patient selection and outlines the procedural techniques employed in CRFA for knee OA. Understanding the factors influencing procedural success will contribute to the refinement of CRFA as a minimally invasive and effective intervention for knee OA.

1) Patient selection criteria

A comprehensive clinical evaluation is fundamental in identifying candidates for treatment. Patients with knee OA who have not responded to conservative treatment and continue to experience persistent pain and functional impairment are potential candidates for further interventions [11,19]. Suitable indications for these treatments in patients who are unable or unwilling to undergo total knee arthroplasty include morbid obesity (body mass index ≥ 35 kg/m^2), heart disease, or mental health issues [19,36]. Additionally, radiographic evidence of knee OA (Kellgren–Lawrence grades: 2–4) includes joint space narrowing, osteophyte formation, a pseudocystic area with sclerotic walls, and deformity of the bone contour [11]. Although this review primarily deals with pain caused by knee OA, CRFA has also been shown to be effective for pain that persists after total knee replacement [37,38].

A thorough pre-procedural assessment, including the identification of contraindications or heightened risk factors, is also crucial for mitigating adverse events. Contraindications include local infection and bleeding tendency. If the patient is taking anticoagulation medications, it should be discontinued for an appropriate period of time prior to the procedure [39]. For patients with a cardiac pacemaker, it should be converted to a fixed-rate pacing during the radiofrequency procedure. Obtaining informed consent and outlining the potential risks and benefits of CRFA are also essential.

2) Diagnostic nerve blocks

Initially, the treatment of the SLGN, SMGN, and IMGN was advised, but recent developments advocate for addressing the suprapatellar GN in the presence of predominant anterior knee pain [11,30,40]. The suprapatellar GN block is performed by inserting the needle 3 cm above the superior patella at the midline of the anterior distal femoral diaphysis [41]. Patients receive diagnostic GN blocks, which can be performed under fluoroscopic or ultrasound (US) guidance (**Fig. 3**), to evaluate their eligibility for the CRFA procedure [42]. Detailed imaging techniques, including fluoroscopy and US, assist in identifying optimal target regions, ensuring that the treatment is precisely directed.

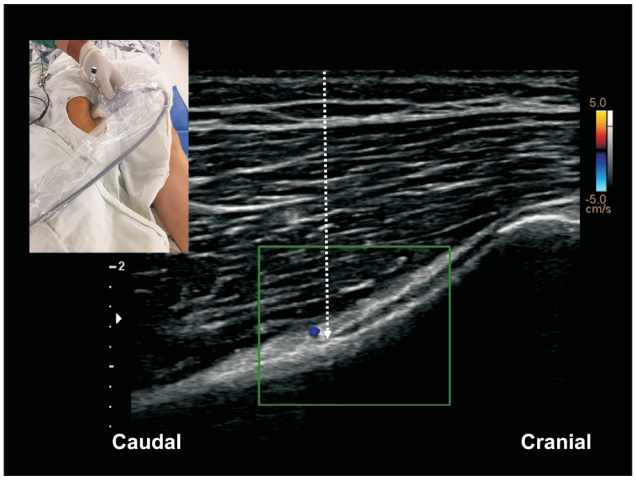

Fig. 3. Ultrasound-guided superior medial genicular nerve block. Representative longitudinal images of the right knee at the level of the distal femoral epicondyle and medial metaphysis of femur is shown. The superior medial genicular nerves accompany each the superior medial genicular artery which is identified using color Doppler mode. Dashed arrow indicates the out-of-plane needle pathway for the superior medial genicular nerve block.

(1) Patient positioning and preparation

Patients are typically positioned to optimize access to the target region while ensuring comfort and safety during the procedure. On the procedure table, patients are placed supine with their symptomatic knee flexed at a 30° angle [42]. A sterile preparation is typically performed for this procedure. The administration of local anesthesia at the entry site and along the planned target region minimizes discomfort during the procedure. Applying 1 mL of 2% lidocaine topically, sufficient to create a skin wheal, effectively induces skin anesthesia at each nerve site.

(2) Diagnostic nerve block

The targets of the SLGN, SMGN, and IMGN blocks are the periosteal areas that connect the femoral shaft to the bilateral epicondyles and the tibial shaft to the medial epicondyle (the epicondyles of the femur and tibia, where the metaphyseal-to-epiphyseal junctions are located, respectively) [11,19,36]. Under fluoroscopic guidance,

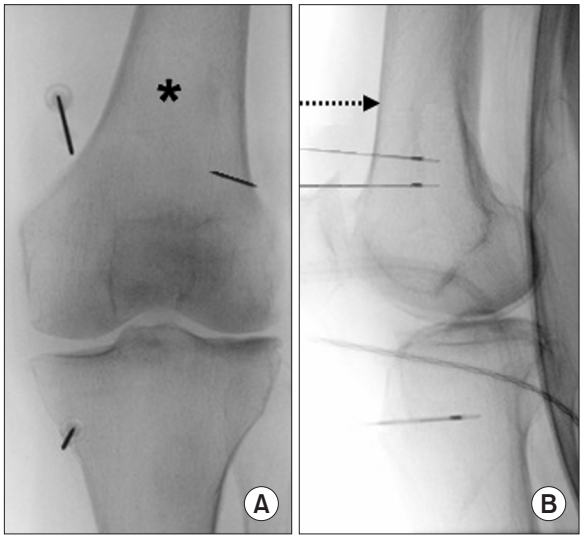

Fig. 4. Fluoroscopic images of the cooled radiofrequency ablation for genicular nerves of the left knee. (A) Anteroposterior fluoroscopic view after cannula insertion for the placement of cooled radiofrequency electrodes into the junction between the shaft and epicondyle of the tibia and femur. (B) Location of electrodes for the cooled radiofrequency ablation of genicular nerves in the lateral fluoroscopic image. Optionally, the suprapatellar genicular intervention can be performed by inserting the needle 3 cm above the superior patella border at the midline of the anterior distal femoral diaphysis (asterisk). Dashed arrow indicates the needle pathway for the suprapatellar genicular intervention.

the procedure should always start in the anteroposterior (AP) view (**Fig. 4A**). A true AP view is identified by the patella at the midline, and the tibiofemoral joint appears symmetrical and at its widest. The needles are inserted at the point where the shaft and epicondyle meet in the AP view and advance to the midpoint of the long axis of the long bone shaft in the lateral view. However, the exact needle placement for GN intervention [32,43–45] requires further research for clarification. US can also be used to guide diagnostic GN blocks [46,47], although this method is not elaborated in this review. For diagnostic blocks, 1–2 mL of either 0.25% bupivacaine or 1% lidocaine is injected at each site [11,19,42]. If there is a 50% or greater reduction in pain score after 15 minutes, 6 hours, or 24 hours, a CRFA procedure is recommended 3–4 weeks later [11,19,36,41,42,48].

3) CRFA electrode placement

The CRFA electrode, equipped with cooling technology, is positioned under guidance to target specific nerves that contribute to knee pain. The preparation for CRFA is the same as the diagnostic nerve block, followed by sedation, if necessary, and monitoring of vital signs. To ensure adequate conduction of the CRFA, a grounding pad is positioned ipsilateral to the joint receiving the CRFA to avoid areas of edema, significant scar tissue, bony prominences, or metal prostheses [42]. After sterile preparation and local anesthesia of the procedure sites, a 50–150 mm 17-G introducer needle is inserted into the IMGN, SLGN, SMGN (**Fig. 4A**), and, if required, the suprapatellar GN under fluoroscopic guidance. The correct placement of the cannula (introducer) is determined using lateral and AP views of fluoroscopy. Following confirmation of the proper position of the cannula, an 18-G internally cooled RFA electrode with a 4 or 5.5 mm active tip is inserted through the introducer needle (**Fig. 4B**). Sensory stimulation is desirable prior to ablation, but not mandatory. To ensure the correct placement of the electrode in the targeted GN, a sensory test is conducted at 50 Hz and < 0.5 V, typically causing mild pain or a pressure sensation in the patient. Prior to the actual ablation, motor nerve activity is excluded by applying 2 Hz at 1 mA. If muscle twitching indicates motor activity, the electrode is repositioned within the introducer, and motor nerve activity is re-evaluated. For deeper anesthesia during CRFA, 1–2 mL of 2% lidocaine is injected through an introducer needle. Each nerve is ablated for 150–180 seconds at 60°C [19,36,37,40,42]. To confirm whether an appropriate effect has occurred, it is performed while monitoring sensory and motor stimulation or patient feedback.

4) Post-ablation procedures and follow-up evaluation

After the completion of CRFA, glucocorticoids can be injected through each cannula to decrease postoperative pain and possible neuritis. It's crucial to monitor patients and provide appropriate post-procedural care, which includes pain management and checking potential adverse events. To ensure that no problems develop and patients remain hemodynamically stable, they are monitored for up to two hours after all suitable sites are ablated [19]. Patients are instructed to avoid heavy lifting for the first week, refrain from underwater submersion for at least 3 days, and gradually resume normal physical activity over a period of up to 2 weeks. Additionally, for one month after the procedure, patients are recommended to abstain from running and stair exercises.

Pain at rest, during activity, and at night, as well as functional status are evaluated during the follow-up visit after the procedure. The Western Ontario and McMaster Osteoarthritis Index (WOMAC), Oxford Knee Score (OKS),

and Knee Injury and Osteoarthritis Outcome Score are common patient-reported questionnaires that determine the overall function and pain levels. Subscales that measure pain, function in sports and recreation, daily life activities, and quality of life (QOL) are also included in these assessments [49].

5) Factors influencing procedural success

Procedural success is often influenced by an operator's experience and skills. Adequate training and proficiency in CRFA techniques contribute to favorable outcomes. Additionally, patient cooperation during the procedure, especially in terms of providing feedback, can enhance the accuracy of electrode placement and the precision of the lesioning process.

4. Clinical efficacy of CRFA for knee OA

As conventional treatments often fail to provide long-lasting relief, the need for innovative interventions arises. The exploration began with a 2015 case report [38] demonstrating that CRFA was effective in patients with chronic knee pain. Since then, many case reports, retrospective studies, and prospective studies have been published (**Tables 1, 2**) [15,38,50–64]. This section discusses the growing body of evidence surrounding the clinical efficacy of CRFA for knee OA, covering various aspects such as pain relief, symptom management, functional improvement, patient-reported outcomes, long-term follow-up, and comparative analysis.

1) Pain relief and functional improvement

Numerous clinical trials and observational studies have documented significant reductions in pain following CRFA procedures [15,38,50–53,55–59,61,62,64]. Patients often experience a notable decrease in knee pain, leading to improved QOL and enhanced mobility [38,52]. The duration of pain relief and its long-term sustainability are critical considerations that shape the overall efficacy of CRFA as a therapeutic intervention [53,59,61].

Studies indicate that patients undergoing CRFA for knee OA often experience improvements in joint function and an increased range of motion [38,50,52,55,56,58]. These functional enhancements contribute to the restoration of daily activities and may alleviate the functional limitations caused by OA, thereby enhancing the overall patient well-being.

2) Patient-reported outcomes

The evaluation of CRFA's clinical efficacy also encompasses patient-reported outcomes, which reflect the subjective experiences and perceptions of individuals who have undergone the procedure. Validated assessment tools and surveys reveal that these patients frequently report high satisfaction levels with CRFA. They commonly cite notable improvements in pain relief, function, and overall QOL [15,51,55,56].

3) Long-term follow-up

An exploration of CRFA's clinical efficacy necessitates the consideration of its long-term outcomes. Longitudinal studies, which tracked patients over extended periods, have provided insights into the durability of pain relief, functional improvements, and potential recurrence of symptoms. For example, Davis et al. [15] compared the effectiveness of CRFA with that of IAS injection six months after implementation. In a subsequent study, they followed patients who underwent CRFA for 12 months, and they found that 65% of the patients had a pain score reduction of 50% or more, which was sustained at 12 months [55]. Additionally, Wu et al. [59] also evaluated the effectiveness of CRFA over a 12-month period and found that its efficacy was comparable to that of RFA. Moreover, Caragea et al. [64] analyzed the effectiveness of CRFA over an average of 23.3 months and reported that 47.8% of patients experienced a 50% or greater reduction in pain intensity on a numerical rating scale (NRS). Such long-term follow-up data are crucial for developing a comprehensive understanding of CRFA's roles in the management of knee OA.

4) Comparative analyses

Comparative analyses with other interventions for knee OA are also essential in evaluating the clinical efficacy of CRFA. Studies that compare CRFA with traditional treatments, such as IAS injections, hyaluronic acid (HA), and conventional RFA, are instrumental in understanding its relative effectiveness.

(1) CRFA *versus* IAS injection

In a prospective, multicenter, randomized controlled trial (RCT), Davis et al. [15] compared CRFA with IAS injections. A total of 151 patients were enrolled, and the NRS, OKS, and Global Perceived Effect (GPE) were employed

 https://doi.org/10.3344/kjp.23344

Table 1. Summary of prospective studies on the effectiveness of the cooled radiofrequency treatment in patients with chronic knee pain

Author, year	Study design	Patient	Groups	Outcome measures	Results	Complications	Comments
McCormick et al., 2017 [51]	Cross-sectional study	Knee OA and 50% or greater pain relief following GN blocks	CRFA (n = 33, 52 discrete knees)	NRS, MQSIII, and PGIC	35% resulted in a 50% or greater reduction in NRS scores, reductions of 3.4 or more points in MQSIII scores, and "very much improved/ improved" PGIC scores. 19% resulted in complete pain relief at a minimum of six months of follow-up.	No serious adverse events	
Davis et al., 2018 [15]	Multicenter, cross-over, RCT	Chronic knee pain (OA)	CRFA (n = 76) IAS (n = 75)	NRS, OKS, GPE, and analgesic drug use at 1, 3, and 6 mo	The CRFA group had more favorable outcomes in NRS at 6 mo: pain reduction, 50% or greater (74.1% *vs.* 16.2%); mean NRS score reduction, 4.9 ± 2.4 *vs.* 1.3 ± 2.2; mean OKS, 35.7 ± 8.8 *vs.* 22.4 ± 8.5; mean improved GPE, 91.4% *vs.* 23.9%; mean changes in nonopioid medication use, CRFA > IAS.	No serious adverse events	
Davis et al., 2019 [55]	Multicenter, cross-over, RCT	Chronic knee pain (OA)	CRFA (n = 58) IAS (n = 4) XO (IAS → CRFA, n = 58)	NRS, OKS, GPE, and analgesic drug use at 12 mo	At 12 mo, 65% of the original CRFA group had pain reduction ≥ 50%, and the mean overall drop was 4.3 points on NRS. In addition, 75% reported' improved' effects. The cross-over group demonstrated improvements in pain and functional capacity.	No serious adverse events related to CRFA	The XO group was a group that performed CRFA in the IAS group in the previous study.
Walega et al., 2019 [54]	Randomized sham-controlled trial	Postoperative pain after TKA	CRFA (n = 35) Sham (n = 32)	Opioid consumption, MQSIII, WOMAC, HADS, SF-12, and McGill Pain Questionnaire score	No difference in opioid consumption, postoperative analgesia side effects, and MQSIII for 48 hr, no difference in physical functioning for 2 d, and no difference in any outcome measure at 1, 3, or 6 mo.	No adverse events	Cooled RFA of the superior lateral, superior medial, and inferomedial genicular nerves when performed 2–6 wk prior to elective TKA
Chen et al., 2020 [56]	Multicenter RCT	Chronic knee pain (OA)	CRFA (n = 88) HA (n = 87)	NRS, WOMAC, GPE, EQ-5D-5L, and safety at 1, 3, and 6 mo	Successful responders (≥ 50% reduction in NRS) (CRFA *vs.* HA): 71% *vs.* 38%. Mean NRS reduction at 6 mo: 4.1 ± 2.2 *vs.* 2.5 ± 2.5. Mean WOMAC improvement at 6 mo: 48.2 *vs.* 22.6. GPE improvement at 6 mo: 72% *vs.* 40%.	CRFA *vs.* HA: 19% *vs.* 14%	
Vallejo et al., 2023 [62]	Double-blind RCT	Chronic knee pain (OA)	CRFA (n = 49) MRFA (n = 47)	VAS, WOMAC, OKS, 5-point Likert scale, and adverse events during 52 wk (1, 4, 12, 24, 52)	Effective for 52 wk in both groups. CRFA seemed to be better sustained beyond 24 wk than MRFA (no significant difference at any time point).	Moderate worsening of knee pain 1 in the CRFA group and 2 in the MRFA group	
Vanneste et al., 2023 [63]	Multicenter double-blind, noninferiority, and pilot RCT	Knee OA, PPSP after TKA	RFA (n = 24) CRFA (n = 25)	Responder at 3 mo, knee pain, functionality, QOL, emotional health, and adverse effect at 6 mo	Successful responders: 17% *vs.* 33% (no significant difference). Inconclusive for noninferiority.	Subcutaneous hematoma (3), infrapatellar hypoesthesia (1), and transient increase in pain (2) in the CRFA group. Transient increase in pain (5) in the RFA group.	Insufficient sample size (pilot trial) Low statistical power

CRFA: cooled radiofrequency ablation, EQ-5D-5L: EuroQol-5 Dimensions-5 Level, GN: genicular nerve, GPE: Global Perceived Effect, HA: hyaluronic acid, HADS: Hospital Anxiety and Depression Inventory scores, IAS: intra-articular steroid, MRFA: monopolar radiofrequency ablation, MQSIII: medication quantification scale III, NRS: numeric rating scale, OA: osteoarthritis, OKS: Oxford Knee Score, PGIC: patient global impression of change, PPSP: persistent postsurgical pain, QOL: quality of life, RCT: randomized clinical trial, RFA: radiofrequency ablation, SF-12: 12-Item Short Form Health Survey, TKA: total knee arthroplasty, VAS: visual analog scale, WOMAC: Western Ontario McMaster Universities Osteoarthritis index.

https://doi.org/10.3344/kjp.23344

Table 2. Summary of retrospective studies on the effectiveness of the cooled radiofrequency treatment in patients with chronic knee pain

Author, year	Study design	Patient	Groups	Outcome measures	Results	Complications	Comments
Menzies and Hawkins, 2015 [38]	Case report	Failed TKA	n = 1	OKS	Pain relief and better knee function up to 9 and 6 mo for the left and right knees, respectively. Significant improvement in QOL, less reliance on analgesics, and ability to walk more freely, including on stairs.	Not reported	
Bellini and Barbieri, 2015 [50]	Case series	Chronic knee pain (OA)	n = 9	VAS, WOMAC for 12 mo	Improvement in VAS pain scores: 2 ± 0.5 at 1 mo, 2.3 ± 0.7 at 3 mo, 2.1 ± 0.5 at 6 mo, and 2.2 ± 0.2 at 12 mo after the procedure and WOMAC scores: 20 ± 2 at 1 mo, 22 ± 0.5 at 3 mo, 21 ± 1.7 at 6 mo, and 20 ± 1.0 at 12 mo.	No adverse event	
Rojhani et al., 2017 [52]	Case report	End-stage knee OA	n = 1	NRS, SF-36, WOMAC	NRS were 0, and WOMAC scores were 22 and 26 at 6 and 12 wk, respectively. It markedly improved function and enhanced QOL.	No adverse event	
Kapural et al., 2019 [53]	Retrospective cohort	Chronic knee pain from OA and after TKA	n = 183	VAS, responders	Average pain reduction: 8.5 → 4.2 > 50% pain reduction: 65% (for 12.5 mo) ≥ 2 of VAS decrease: 77% Mean duration of > 50% reduction: 12.5 mo No decrease in opioid use	No adverse event	
Eshraghi et al., 2021 [57]	Retrospective analysis	Chronic knee pain (OA)	n = 104	PDI score, NPRS, MED at 3 mo	After CRFA, 67.3% of patients had a decrease in PDI scores, with a mean reduction of 31.5%; 27.9% had no change, and 4.8% had an increase; 93% of patients had a reduction in NPRS scores, and 50% of patients had a pain score reduction of 2.2 points. The MED did not change in 80.7% of patients.	No adverse event	
Kocayiğit et al., 2021 [58]	Retrospective	Chronic knee pain (OA)	CRFA (n = 29) RFA (n = 34)	VAS and WOMAC at 0, 2, 6, and 12 wk	The mean VAS scores in the CRFA and RFA groups were 8.97 *vs*. 8.44 at baseline and 4.79 *vs*. 4.94 at 12 wk. The WOMAC scores were 67.14 *vs*. 62.03 at baseline and 45.14 *vs*. 38.21 at 12 wk. However, there was no statistically significant difference between the two techniques.	One hematoma	No description of complications is the CRFA or RFA group.
Wu et al., 2022 [59]	Retrospective cohort	Chronic knee pain (OA)	CRFA (n = 104) RFA (n = 104)	Responder (reduction in NRS ≥ 2) for 12 mo (1, 3, 6, 9, and 12), duration of relief, and TKA within 1 yr of treatment	Both RFA and CRFA effectively reduced NRS pain scores in most patients. RFA was associated with a higher probability of treatment success and a greater degree of pain relief at 1 mo after the procedure compared to CRFA.	One cellulitis in the RFA group	
Kapural et al., 2022 [61]	Retrospective, single center	Chronic knee pain (OA)	RFA (n = 170) CRFA (n = 170)	VAS, duration of pain reduction	VAS at 4–6 wk decreased to 5.07 ± 2.8 for RFA and 4.26 ± 3.2 for CRFA. The difference was profound and significantly better in favor of CRFA as the duration of reduction of pain scores by greater than 50% was 2.6 mo for RFA and 11.1 mo for CRFA. Only 15 patients (8.8%) continued to receive > 50% of pain relief in RFA at 12 mo, as compared to 78 (46%) at 12 mo for CRFA.	Not reported	
Caragea et al., 2023 [64]	Cohort study	Chronic knee pain (OA)	CRFA (n = 129) RFA (n = 5)	NRS, proportion of treatment success, PGIC	Mean follow-up time: 23.3 mo ≥ 50% NRS reduction: 47.8% (n = 64) 2-point NRS score reduction: 61.2% (n = 82) "Much improved" on the PGIC: 59.0% (n = 79)	No adverse event	

CRFA: cooled radiofrequency ablation, MED: morphine equivalent dose, NPRS: numerical pain rating scale, NRS: numerical rating scale, OA: osteoarthritis, OKS: Oxford Knee Score, PDI: pain disability index, PGIC: patient global impression of change, QOL: quality of life, RFA: radiofrequency ablation, SF-36: 36-Item Short-Form Health Survey, TKA: total knee arthroplasty, VAS: visual analogue scale, WOMAC: Western Ontario McMaster Universities Osteoarthritis Index.

to evaluate outcomes over a 6-month period. Results showed that the CRFA group had better outcomes than the IAS group at 6 months in terms of pain reduction (74.1% in CRFA *vs*. 16.2% in IAS, achieving 50% or more reduction, $P < 0.001$), mean NRS score reduction (1.3 ± 2.2 in CRFA *vs*. 4.9 ± 2.4 in IAS, $P < 0.001$), mean OKS improvement (22.4 ± 8.5 in CRFA *vs*. 35.7 ± 8.8 in IAS, $P < 0.001$), and improved GPE (91.4% in CRFA *vs*. 23.9% in IAS, $P < 0.001$) [15].

(2) CRFA *versus* HA injection

In a multicenter RCT, Chen et al. [56] compared CRFA with HA injections. A total of 175 patients were enrolled, and the NRS, WOMAC, GPE, and EuroQol-5 Dimensions-5 Levels were used to assess outcomes over a 6-month period. The study found that 71% of the patients in the CRFA group and 38% in the HA group achieved a reduction of ≥ 50% in the primary end point, the NRS pain score ($P < 0.001$). The mean NRS score reduction at 6 months was 4.1 ± 2.2 for CRFA and 2.5 ± 2.5 for HA ($P < 0.001$). Additionally, the mean WOMAC score improvement at 6 months from baseline was 48.2% for CRFA and 22.6% for HA ($P < 0.001$). Furthermore, after 6 months, 72% of the participants in the CRFA group reported an increase in their GPE score, while only 40% in the HA group reported the same improvement ($P < 0.001$) [56].

(3) CRFA *versus* conventional RFA

Several prospective and retrospective studies have compared CRFA with conventional RFA [58,59,61–63]. Most of these studies have concluded that the clinical effectiveness of CRFA is comparable to [58,62,63] or better than that of conventional RFA [59]. Although all prospective studies published in 2023 found no statistically significant difference between CRFA and conventional RFA [62,63], a pilot study by Vanneste et al. [63] with a small sample size revealed a notably higher responder rate (50% or greater effect) in the CRFA group than in the conventional RFA group at the 6 month follow-up. In addition, a retrospective study by Kapural et al. [61] reported that the duration of pain score reduction by more than 50% was 2.6 months for conventional RFA and 11.1 months for CRFA, indicating a significant difference ($P < 0.001$) in favor of CRFA.

5. Safety and adverse events of CRFA for knee OA

1) Safety profile

CRFA is designed to have a localized effect, targeting specific nerves in the knee joint while minimizing damage to the surrounding tissues [17,18]. This specificity contributes to its favorable safety profile compared with that of more invasive procedures. The integration of cooling technology in CRFA ensures precise temperature control during the ablation process and minimizes the risk of excessive thermal injury, thereby enhancing the safety of the procedure [17,18].

2) Adverse events

Most published studies have not reported any serious adverse events associated with CRFA [15,50–55,57,64], and the documented adverse events are generally nonserious and transient [58,62,63]. Patients may experience temporary discomfort or pain at the site of electrode insertion [62,63], as well as hematoma and infrapatellar hypoesthesia [58,63]. These side effects are typically self-limiting and can be managed with analgesics. Notably, there have been reports of septic OA following CRFA [65] and cellulitis following conventional RFA [59]. In addition, while skin burns have been observed in conventional RFA of the IMGN [66], such incidents have not been reported for CRFA. However, there may be a risk of skin burns after CRFA because the lesion size in CRFA is larger than that in conventional RFA. In particular, when performing CRFA on superficial targets, such as the IMGN, special caution is advised because of the thin skin. Additionally, if the patient complains of severe pain during CRFA, the procedure may be considered for conversion from CRFA to pulsed radiofrequency [67].

3) Long-term considerations

Although CRFA can provide significant and sustained pain relief, there is a potential for symptom recurrence over time. Long-term follow-up studies are important to understand the durability of treatment effects, so further research is needed.

6. Future directions and advancements in CRFA for knee OA

CRFA can alleviate chronic pain caused by knee OA for a relatively long time, thereby improving the function and

QOL. Although CRFA appears to be an effective treatment for chronic knee pain, further optimization of this therapy based on recent findings on anatomy, optimal imaging, stimulating patterns, and patient selection may yield even better results and benefit a broader patient population. However, few studies have explored the factors that can predict the positive effects of genicular CRFA. In addition, a consensus regarding the anatomical targets and needle placement is required to maximize the effectiveness of CRFA.

CRFA for knee OA has exciting prospects with potential advancements in personalized approaches, technological innovations, combination therapies, and expanded indications. Ongoing research and technological developments are poised to revolutionize CRFA, thereby improving its effectiveness, expanding its clinical utility, and ultimately elevating the quality of care for individuals with knee OA.

CONCLUSIONS

The clinical efficacy of CRFA for knee OA is characterized by notable pain relief, improved functional outcomes, and positive patient-reported experiences. CRFA for knee OA has demonstrated a generally favorable safety profile, with most adverse events being transient and self-limiting. As more evidence accumulates, further investigations and long-term follow-up studies are expected to enhance our comprehension of CRFA's roles in the management of knee OA. This new paradigm has the potential to transform the treatment of knee OA and provide patients with a viable option to significantly enhance their QOL.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

ACKNOWLEDGMENTS

The authors thank their mentor, Jeong-Gil Leem, MD, PhD (Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine), for his inspiring feedback and encouragement.

FUNDING

No funding to declare.

CONFLICT OF INTEREST

Jin-Woo Shin is an editorial board member, and Seong-Soo Choi is a section editor of the Korean Journal of Pain; however, they have not been involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Myong-Hwan Karm: Writing/manuscript preparation; Hyun-Jung Kwon: Writing/manuscript preparation; Chan-Sik Kim: Data curation; Doo-Hwan Kim: Investigation; Jin-Woo Shin: Supervision; Seong-Soo Choi: Writing/manuscript preparation.

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