Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Ablation of Peripheral Nerves to Treat Pain including Coolief Cooled RF and Iovera System

Description/Background

Radiofrequency ablation (RFA) and cryoneurolysis of nerves have been proposed as treatments for several different types of pain. RFA has been used to treat a number of clinical pain syndromes such as trigeminal neuralgia as well as cervical and lumbar pain. This review evaluates the application of RFA and cryoneurolysis in peripheral sites distant from the spine.

Peripheral Nerve Pain

There are many types of peripheral neuropathy, which can be brought on by diabetes, genetic predisposition (hereditary causes), exposure to toxic chemicals, alcoholism, malnutrition, inflammation (infectious or autoimmune), injury and nerve compression, and by taking certain medications such as those used to treat cancer and HIV/AIDS. When the cause of a person's peripheral neuropathy remains unknown, it is called 'idiopathic.'

Diagnosis

The symptoms of peripheral neuropathy are highly variable. A thorough neurological examination is required to sort out the cause of the symptoms and involves taking an extensive medical history. In addition, tests are usually performed (e.g., nerve conduction velocity, electromyography, nerve biopsy) to identify the cause of the neuropathy as well as the extent and type of nerve damage.

Treatments

Neuropathic pain is often difficult to control. Mild pain may sometimes be alleviated by over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or prescribed medications such as antidepressants, anticonvulsant medications or narcotic agents. Topically administered medications are another option for neuropathic pain. Two agents are topical lidocaine, an anesthetic agent, and capsaicin, a substance found in hot peppers that modifies peripheral pain receptors.

Surgical intervention may be considered for some types of neuropathies. Injuries to a single nerve caused by focal compression may respond well to surgery that releases the nerve from the tissues compressing it. Some surgical procedures reduce pain by destroying the nerve (e.g., thermal [heat or cold], electrical or chemical); this approach may be appropriate only for pain caused by a single nerve and when other forms of treatment have failed to provide relief. Peripheral neuropathies that involve more diffuse nerve damage, such as diabetic neuropathy, are not amenable to surgical intervention.

Chronic Headaches
Numerous treatments for headaches (e.g. migraine, cluster headaches, tension type headaches and cervicogenic headache), occipital neuralgia and persistent idiopathic facial pain (PIFP) (atypical facial pain) have been proposed, with varying levels success. The consensus on standard treatment does not exist, because of the variability in patient selection and clinical outcomes. Pharmacological treatment with oral analgesics, anti-inflammatory medications, tricyclic antidepressants, and anticonvulsant medications have been used alone or in combination with other treatment modalities. Other treatment modalities suggested are: the use of cervical collar during the acute phase; physical therapy with stretching and strengthening exercises; postural training; relaxation exercises; transcutaneous nerve stimulation (TENS); and manual therapy including spinal manipulation and spinal mobilization.

Treatments
Pharmacological and alternative treatment modalities are not effective for all individuals. Therefore, other treatment methods have been proposed, such as cryoneurolysis (cryoablation, cryotherapy or cryoanalgesia), to attempt to denervate the occipital and/or upper cervical nerve(s) for pain relief.

Nerve Radiofrequency Ablation
Nerve radiofrequency ablation (RFA) is a minimally invasive method that involves the use of heat and coagulation necrosis to destroy tissue. A needle electrode is inserted through the skin and then into the tissue to be ablated. A high-frequency electrical current is applied to the target tissue. A small sphere of tissue is coagulated around the needle by the heat generated. It is theorized that the thermal lesioning of the nerve destroys peripheral sensory nerve endings, resulting in the alleviation of pain. Cooled radiofrequency (RF) treatment is a variation of nerve RFA using a special device that applies more energy at the desired location without excessive heat diffusing beyond the area, causing less tissue damage away from the nerve (see Table 1). The goal of ablating the nerve is the same.

Coolief is a cooled radiofrequency (C-RF) device currently being used for RFA of peripheral nerves of the back, hip and knee. Cooled RF devices generate heat using radio waves and are often used for RF denervation (RFD) in nerve tissue. The radio waves are delivered to the targeted nerves via needles inserted through the skin. Sterile water pumped through the device circulates and cools the RF probe, allowing treatment of an area larger than conventional RFD. The tip of the needle heats the surrounding tissue.

For the indications assessed in this evidence review, nerve RFA should be distinguished from RF energy applied to areas other than the nerve to cause tissue damage. Some patients have been treated for plantar fasciitis with a fasciotomy procedure using a RF device. This procedure does not ablate a specific nerve.

Table 1. Types of Radiofrequency Ablation

Type	Procedure	Tissue Temperature	Key Differences
Standard RFA	Electrode tip provides thermal energy for 90 – 130 seconds	70 – 90° C	Longer term pain relief but with more adjacent thermal tissue injury and limitation in size and shape of lesion.
Pulsed RFA	Non-ablative - provides 20 ms pulses every 30 seconds	42° C	Limits tissue damage but results in shorter duration of pain relief.
Cooled RFA	Water circulates through RF electrode to cool the tip	60° C	Larger lesion with limited thermal injury to tissue. Longer term pain relief.

RF: radiofrequency; RFA: radiofrequency ablation
Adapted from Oladeji et al (2019)[2]

Cryoneurolysis

Cryoneurolysis is an alternative analgesic modality that utilizes extremely cold temperatures to reversibly ablate peripheral nerves. This technique has predominantly been used to treat chronic pain, using percutaneous probes and ultrasound guidance. There is a recent development of use with a handheld cryoneurolysis device, which allows for a wider range of clinical applications. Cryoneurolysis has been utilized for treatment of lower back pain, neck pain, neuromas, and intercostal neuralgia. It is being investigated as a possible treatment option for peripheral neuropathies and neuromas, as well as for pain control for knee osteoarthritis and following a thoracotomy.

Cryoneurolysis is being investigated to alleviate pain using cold temperature settings. Temperatures of -20° to -100°C applied to a nerve cause Wallerian (anterograde axonal) degeneration, with disruption of nerve structure and conduction but maintenance of the perineural and epineural elements of the nerve bundle. Wallerian degeneration allows complete regeneration and recovery of nerve function in about 3 to 5 months. The iovera° system is a portable handheld device that applies percutaneous and targeted delivery of cold to superficial peripheral nerves. Highly pressurized liquid nitrous oxide travels through the handpiece to the closed end needles of the Smart Tip, where it undergoes a phase change and becomes very cold. This phase change forms a precise cold zone in the tissue causing a temporary nerve block.

While cryoablation is similar to cryoneurolysis in that they both incorporate extreme cold, cryoablation destroys nerve endings and creates a permanent nerve block. Cryoablation devices have been identified as cryosurgical by the FDA, which is a different device identification than cryoneurolysis devices (FDA, 2019a).

Regulatory Status

A number of radiofrequency (RF) generators and probes have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Some examples are listed in Table 2.

Although cryoablation equipment (e.g., IceRod CX cryoablation probe, IceEDGE 2.4, Visual-ICE™) have all received U.S. Food and Drug Administration (FDA) 510(k) marketing clearance, none appear to be specifically indicated for treatment of peripheral nerve pain.

In 2014, the iovera system Pacira (formerly Myoscience, Inc) received 510K clearance from the U.S. Food and Drug Administration (FDA). It is cleared to be used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by application of cold to selected site for blocking of pain. The iovera device is not indicated for the treatment of central nervous system tissue.

In 2017, the COOLIEF Cooled Radiofrequency Probe (Avanos, previously known as Halyard Health) was cleared for marketing by the FDA through the 510(k) process to be used in conjunction with a radiofrequency generator to create lesions in nervous tissue (K163461). One of the indications is specifically for "creating radiofrequency lesions of the genicular nerves for the management of moderate to severe knee pain of more than 6 months with conservative therapy, including medication, in patients with radiologically-confirmed osteoarthritis (grade 2-4) and a positive response (>50% reduction in pain) to a diagnostic genicular nerve block."

Table 2. Radiofrequency and Cryoneurolysis Devices

Device	Manufacturer	Clearance	Date	FDA Product Code
SInergy®/Bayless Pain Management Probe	Kimberly-Clark/Baylis	K053082	2005	GXD
NeuroTherm® NT 2000	NeuroTherm	K111576	2011	GXD
iovera	Pacira (formerly Myoscience)	K133453	2014	GXH
COOLIEF® Cooled Radiofrequency Kit	Avanos, (formerly Halyard Health)	K163236	2016	GXI
COOLIEF® Cooled RF Probe	Avanos, (formerly known as Halyard Health)	K163461	2017	GXI
Rulo(TM) Radiofrequency Lesion Probe	Epimed International	K190256	2019	GXI
Coolief Cooled Radiofrequency Kit Advanced	Avanos, (formerly known as Halyard Health)	K203066	2020	GXI
Coolief Radiofrequency Generator (CRG) System	Avanos, (formerly known as Halyard Health)	K192491	2020	GXI
Intracept Intraosseous Nerve Ablation System	Relievant Medsystems, Inc	K222281	2022	GXI
Apex 6 Radiofrequency Lesion Generator	RF Innovations, Inc	K220122	2023	GXD

Medical Policy Statement

Radiofrequency ablation of peripheral nerves to treat pain (e.g., plantar fasciitis, occipital neuralgia, cervicogenic headache, osteoarthritis, etc.) is **experimental/investigational**. It has not been scientifically demonstrated to improve patient clinical outcomes.

Cryoablation for the treatment of peripheral neuropathy is **experimental/investigational**. It has not been scientifically demonstrated to improve patient clinical outcomes.

Cryoneurolysis of peripheral nerves to treat pain associated with knee osteoarthritis, cervicogenic headache, or total knee arthroplasty is **experimental/investigational.** It has not been scientifically demonstrated to improve patient clinical outcomes.

Ablation of peripheral nerves to treat pain is **experimental/investigational** in all other conditions with the exception of facet joint pain. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0440T	0441T	0442T	64624*	64625*	64640*

This code is not covered when used for the procedures discussed within this policy.

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at Blue Cross or BCN to verify coverage.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or

worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

RADIOFREQUENCY ABLATION [RFA, including cooled RF] For OSTEOARTHRITIS (Knee, Hip)

Clinical Context and Therapy Purpose

The purpose of RFA in individuals with knee osteoarthritis (OA) who have severe refractory pain is to provide a treatment option that is an alternative to intra-articular injections or total joint replacement. Pain in OA can be transmitted via the genicular sensory nerves, which are branches of the femoral, tibial, peroneal, saphenous, and obturator nerves around the knee.[2] The genicular nerve branches can be divided into a four-quadrant system — superomedial, superolateral, inferomedial, and inferolateral. Nerves in the superomedial, superolateral, and inferomedial quadrants are located near the periosteum, but the inferolateral branch is close to the peroneal nerve and is usually avoided. The exact neuroanatomy around the knee is variable and can also be affected by chronic OA. Although the location of the target nerves is aided by palpating the bony landmarks and with the use of fluoroscopy, variability may prevent the exact localization. Diagnostic nerve blocks have been evaluated to confirm the location of the genicular nerves and predict efficacy. In addition to the genicular nerves, studies have reported RFA of the saphenous nerve, the sciatic nerve, the femoral, tibial, saphenous nerves, and peripatellar plexus in combination, and the intra-articular joint space.[3]

The following **PICO** was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with knee osteoarthritis.

Knee and hip osteoarthritis is common, costly, and often the cause of substantial disability. Prevalence increases with age, from about 24% among those 60 to 64 years of age to as high as 40% in those 70 to 74 years of age.[33] Knee osteoarthritis is characterized by pain upon initiation of movement or walking. As osteoarthritis progresses, the pain becomes continuous and joint functionality is severely impaired. Hip join pain is characterized by groin pain with radiation to the buttocks or upper-outer thigh.

Interventions
The therapy being considered is RFA of the superomedial, inferomedial, and superolateral genicular nerves. Due to the variable location of the genicular nerves, it is thought that the increased area of denervation associated with cooled-RFA may be more effective than standard or pulsed RFA.

Comparators
The following therapy is currently being used to make decisions treating osteoarthritis: conservative management, which may include analgesics, physical therapy, or intra-articular injections.

Treatment for OA of the knee aims to alleviate pain and improve function. However, most treatments do not modify the natural history or progression of OA and are not considered curative. Nonsurgical modalities used include: exercise; weight loss; various supportive devices; acetaminophen or nonsteroidal anti-inflammatory drugs (e.g., ibuprofen); nutritional supplements (glucosamine, chondroitin); and intra-articular viscosupplements. Corticosteroid injection may be considered when relief from nonsteroidal anti-inflammatory drugs is insufficient, or the patient is at risk of gastrointestinal adverse events. If symptom relief is inadequate with conservative measures, invasive treatments may be considered. Total knee arthroplasty is an operative treatment for symptomatic OA of the knee.

Outcomes
The most clinically relevant outcome measures for pain treatments are measures of pain severity and functional limitations. Pain is a subjective, patient-reported measure. Therefore, pain outcomes require quantifiable pre- and posttreatment measures. Pain is most commonly measured with a visual analog scale (VAS) or 11-point numeric rating scale (NRS).

The Oxford Knee Score is scaled between 12 and 60, with 12 representing the best outcome. Quantifiable pre- and post-treatment measures of functional status are also used, such as the 12-Item and 36-Item Short-Form Health Survey.

The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) is also frequently used to evaluate function due to osteoarthritis. The WOMAC includes 3 subscales: pain, stiffness, and physical functioning. Scores range from 0 to 96, with higher scores indicating greater disability.

The Lysolm Knee Score (LKS) has 8 domains to assess limitations in function, including limp, use of supports, locking, instability, pain, swelling, stair-climbing, and squatting. Scores range from 0 to 100, with lower scores indicating greater disability.

Because of the variable natural history of osteoarthritis and the subjective nature of the outcome measures, RCTs are needed to determine whether outcomes are improved with interventions for pain. Trials should include a homogenous population of individuals with a defined clinical condition, use standardized outcome measures when possible, and define a priori the clinically significant magnitude of response.

The effect of RFA is likely to be transient, so the period for follow-up is within a month to determine procedural success and at least one year to evaluate durability. Longer follow-up is needed to evaluate whether denervation of sensory nerves of the knee could have adverse long-term effects on knee anatomy in individuals with OA.

Study Selection Criteria

We selected methodologically credible studies, using these principles:

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with a preference for RCTs with a minimum of six months outcomes, and systematic reviews of RCTs
- To assess long-term outcomes and adverse effects, we sought single-arm studies with longer periods of follow-up and/or larger populations.
- Within each category of study design, we included studies with larger sample sizes and longer duration.

Systematic Reviews

Characteristics of systematic reviews are described in Tables 3 and 4.

Chen et al (2021) conducted a systematic review of RFA for the treatment of knee OA.[4,] The authors (including several affiliated with the American Academy of Orthopedic Surgeons) identified 7 RCTs published through 2019 that met inclusion criteria. Quality of the studies was assessed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for risk of bias of randomization, allocation concealment, blinding, incomplete data, selective reporting, and other bias. Five of the trials were rated as high quality[5,6,7,8,9,] despite lack of blinding in most and moderate risk of bias for allocation concealment and other biases. Two [10,11,] were rated as moderate quality. A majority of the studies were conducted outside of the U.S., with a number of participants ranging from 24 to 151. Techniques included RFA and cooled RFA. RFA was compared to non-treated controls or sham procedures, intra-articular corticosteroids, or hyaluronic acid. There was high heterogeneity due to the variability in comparators and outcome measures that limited meta-analysis, but analysis of the mean differences for the individual studies showed general agreement that RFA had a benefit on pain, function, and composite scores compared to the control treatments at 3 and 6 month follow-up.

Liu et al (2022) performed a systematic review of RFA, pulsed RF, C-RFA, and RF thermocoagulation to either the genicular nerve or intra-articular nerves in patients with knee OA.[36] The authors identified 15 RCTs which met their inclusion criteria. This assessment concluded that all studies had a low risk of bias for random sequence generation, 12 (80%) had a low risk of bias for allocation concealment, 6 (40%) had a low risk of bias for blinding of participants, and personnel as well as blinding of outcome assessment. A low risk of selective reporting was identified in 12 (80%) studies, and all studies were reported as having a low risk of other biases. No overall assessment of study quality was provided. The authors reported a mean pain score difference in favor of the radiofrequency group over the control group at 1 to 2 weeks (-1.72; 95% confidence interval [CI], -2.14 to -1.30), 4 weeks (-1.49; 95% CI, -1.76 to -1.21), 12 weeks (-1.83; 95% CI, -2.39 to -1.26), and 24 weeks (-1.96; 95% CI, -2.89 to -1.04); however, all these estimates had significant heterogeneity ranging from 66% to 97% (p<.00001). A subgroup analysis limiting the site of radiotherapy to the genicular nerve included 5 trials and found a weighted mean difference between RF and control of -1.64 (95% CI, -2.19 to -1.09; p<.001) with a high level of heterogeneity (I2, 84%; p<.001) at 1 to 2 weeks

post-treatment. The mean difference in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores also favored the radiofrequency group over control groups at 4 weeks (-10.64; 95% CI, -13.11 to -8.17), 12 weeks (-6.12; 95% CI, -7.67 to -4.57), and 24 weeks (-10.89; 95% CI, -12.28 to -9.51). No significant heterogeneity was observed in the 4 and 12 week WOMAC score pooled estimates, but the evidence was limited to being pooled from 4 trials. The rate of adverse events appeared equivalent between groups when observed when pooling data from 13 RCTs (risk difference, 0.03; 95% CI, -0.01 to 0.06; p=.14) with no significant heterogeneity.

Wu et al (2022) conducted a systematic review and network meta-analysis of multiple RFA modalities versus other treatments for osteoarthritis (OA) with a focus on short-term clinical outcomes through 6 months post-treatment.[37] Twenty-one RCTs were identified that were eligible for inclusion. The evidence base consisted of 1818 individuals with a range of 24 to 260 participants across the included RCTs. Outcomes of interest included VAS Pain and WOMAC function scores as well as adverse events. The authors found that C-RFA has better efficacy for pain and function than conventional or pulsed modalities and that conventional RFA outperforms pulsed RFA. Visual analog scale (VAS) pain scores were reported in 16 studies at 3 months follow-up (n=1401). All interventions, with the exception of exercise, had significant improvement compared with placebo. In a ranked surface under the cumulative ranking curve (SUCRA) analysis, monopolar C-RFA of the genicular nerve ranked first in analgesia performance, followed by conventional monopolar RFA of the genicular nerve, intraarticular platelet-rich plasma injection (IAPRP), pulsed monopolar RFA of the genicular nerve, intraarticular anesthesia injection (IAA), intraarticular dextrose injection (IAD), intraarticular sodium hyaluronate injection (IAHA), pulsed monopolar RFA of the saphenous nerve, intraarticular corticosteroid injection, nonsteroidal anti-inflammatory drugs (NSAIDs). At 6 months, 10 trials reported on 1,021 individuals for VAS pain outcomes. All treatments, save NSAIDs, had a significantly decreased VAS score compared with exercise at 6 months follow-up. A SUCRA analysis showed that the best-performing intervention was conventional bipolar RFA of the genicular nerves (MD, -5.5; 95% CI, -4.3 to -6.7) followed by conventional monopolar RFA of the genicular nerves, pulsed monopolar intraarticular RFA, pulsed monopolar RFA of the genicular nerve, IACS, IAHA, IAPRP, and NSAIDs. WOMAC scores were reported in 14 studies (n=1091) at 3 months and by 9 studies (n=821) at 6 months follow-up. At 3 months, except for exercise, NSAIDs, and pulsed monopolar IPRFA, all treatments had a significant reduction in WOMAC scores compared to placebo. SUCRA analysis suggested the first rank intervention for improved knee performance at 3 months follow-up was cooled monopolar RFA of the genicular nerve followed by conventional bipolar RFA of the genicular nerve, pulsed monopolar intraarticular RFA, conventional monopolar RFA of the genicular nerve, pulsed monopolar intraarticular RFA plus IAPRP, IAA, pulsed monopolar RFA of the genicular nerves, pulsed monopolar IPRFA, IAS, and IAHHA. All interventions had a significant improvement in WOMAC scores at 6 months compared to exercise. SUCRA analysis showed the best performance for cooled monopolar RFA of the genicular nerve followed by conventional bipolar RFA of the genicular nerve, conventional monopolar RFA of the genicular nerve, pulsed monopolar RFA of the genicular nerve, IACS, IAHA, NSAIDs and exercise. The authors also reported that adverse events were recorded in 6 RCTs (n=836) and found 43 (8.3%) in the RFA groups, which were likely attributable to RFA; major adverse events included: pain (n=5), post-procedural pain (n=7), fall (n=5), stiffness (n=1) and swelling (n=2).

The trials by Davis et al (2018), El-Hakeim et al (2018) and Xiao et al (2018) and Chen et al (2021) with 6-month follow-up, along with later RCTs that are not included in the systematic review, are described in greater detail below.

Table 3. Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Chen et al (2021)	1966 - 2019	7	Individuals with OA of the knee who were treated with RFA or C- RFA	NR (24 to 151)	RCT	up to 12 months
Liu et al (2022)	Database inception - 2021	15	Individuals with OA of the knee who were treated with RFA, C-RFA, pulsed radiofrequency, or RF thermocoagulation	1009 (16 to 177)	RCT	up to 24 months
Wu et al (2022)	Database inception - 2021	21	Individuals with OA of the knee who were treated with RFA, C-RFA, pulsed radiofrequency, bi-polar RFA, IAA, IAD, IAPRP, IAHA, intra-articular erythropoietin, IACS, NSAIDs, or exercise	1818 (24 to 260)	RCT	6 months

C-RFA: cooled radiofrequency ablation; IAA: intra-articular anesthesia; IACS: intra-articular corticosteroid; IAD: intra-articular dextrose; IAHA: intra- articular sodium hyaluronate; IAPRP: intra-articular platelet rich plasma; NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; RCT: randomized controlled trial; RF: radiofrequency; RFA: radiofrequency ablation.

Table 4. Comparison of Trials/Studies Included in SR & M-A

Study	Trial Size	Nerve Target	Prognostic Block	RF Method	Comparator	Follow-up	Chen et al (2021)	Liu et al (2022)	Wu et al (2022)
Choi et al (2011)	38	GN	Yes	RFA	Sham	3 months	●	●	●
Yi et al (2012)	36	GN	No	RFA	IA Hyaluronic Acid	3 months		●	
Rahimzadeh et al (2014)	50	IA	No	PRF	IA Sham	3 months		●	●
Hashemi et al (2016)	72	IA+GN	NR	PRF	IA Steroid	3 months			●

Yang et al (2015)	62	GN	No	RFA	IA Hyaluronic Acid	3 months		●	
Hu et al (2016)	92	IA	No	PRF	NSAIDs	6 months		●	
Sari et al (2016)	50	GN	NR	RFA	Ultrasound	3 months			●
Yuan (2016)	24	IA	Yes	PRF	IA Steroid	6 months		●	●
Gulec et al (2017)	100	IA	NR	PRF	Monopolar RFA	3 months			●
Shen et al (2017)	54	IA	No	RFA	Standard Treatments	3 months	●	●	
Sari et al (2018)	73	GN	No	RFA	IA Steroid	3 months	●	●	●
Davis et al (2018)	151	GN	Yes	C-RFA	IA Steroid	6 months	●	●	
El-Hakeim et al (2018)	60	GN	No	RFA	Acetaminophen and NSAIDs	6 months	●	●	●
Jadon et al (2018)	30	GN	NR	RFA	Monopolar RFA	6 months			●
Ray et al (2018)	24	GN	Yes	RFA	IA Hyaluronic Acid	3 months	●		●
Xiao et al (2018)	96	GN	No	RFA	IA Hyaluronic Acid	6 months	●	●	●
Davis et al (2019)	151	GN	NR	C-RFA	IACS	12 months			●
Monerris et al (2019)	28	GN	NR	PRF	Placebo	6 months			●
Kumaran et al (2019)	30	IA	No	RFA	Sham	3 months		●	
Chen et al (2020)	177	GN	Yes	C-RFA	IA Hyaluronic Acid	6 months		●	●
Han et al (2020)	62	GN	NR	C-RFA	Exercise	6 months			●
Hong et al (2020)	53	GN	No	RF thermocoagulation	IA Steroid	6 months		●	

Santana et al (2022)	216	GN	NR	PRF	IA Hyaluronic Acid	12 months			●
Carpenedo (2021)	16	IA	Yes	PRF	Sham PRF	6 months		●	
Abdelraheem et al (2021)	200	GN	NR	PRF	IA-PRP	12 months			

Twelve to 24 month follow-up of a subset of patients treated with RFA in the RCT by Davis et al (2018) was reported by Hunter et al (2020) and is shown in Table 7.[8,14] There were 42 patients randomized to RFA and 41 randomized to the control group who crossed over to RFA at 6 months who qualified for follow-up at participating sites. Of the 83 potential participants, 15 had additional procedures (e.g. steroid injection, total knee arthroplasty, hyaluronic injection, repeat RFA) and were not included in the analysis, 35 (42.2%) could not be reached or declined to participate, and 33 (40%) consented for the study. Although 44% of patients who participated in follow-up maintained their improvement in pain scores, this was a small percentage of the patients who received treatment. Interpretation is limited due to the missing data and potential for bias in this non-blinded study.

Another manufacturer-sponsored trial on cooled RFA for knee osteoarthritis was reported by Chen et al (2020).[15] The investigators randomized 177 patients to RFA or a single injection of hyaluronic acid (Synvisc ONE). Although widely used, the efficacy of hyaluronic acid has not been supported by evidence.[16] Therefore, it might be considered a placebo treatment. Crossovers to RFA (n=68, 82.9%) were allowed at 6 months. A major limitation of this publication is that results were reported only for the 83% of control patients who crossed over; the authors noted that the remainder of the patients reported long-term pain relief from hyaluronic acid. Lyman et al (2022) published an extension study to assess long-term outcomes through 24 months for participants in this trial who received RFA.[38] Of the initial 66 RFA patients who had 12 months follow-up, 36 signed the informed consent to participate in the extension study. Thirty-two of these participants completed 18 month follow-up and 27 completed 24 month follow-up; the primary reason for loss to follow-up was receiving another knee procedure (Table 7). At baseline, the participants had a mean NRS of 6.8±0.8 which was reduced to 2.4 ± 2.5 (64% reduction) at 18 months and 3.4 ± 3.2 (51% reduction) at 24 months; a ≥ 50% improvement in NRS pain scores was experienced by 22 (69%) of patients at 18 and 17 (63%) at 24 months. Mean WOMAC scores at baseline for these participants were 64.4 ± 14.7, which were reduced by a mean of 34.7±27.5 (54%; p<.0001 versus BL) and 24.8±32.8 (35%; p<.0007) at 18 and 24 months respectively. No serious or non-serious adverse events related to cooled RFA were reported by the authors at 18 or 24 months post-treatment.

An independent study by Elawamy et al (2021) compared pulsed radiofrequency to a single injection of platelet-rich plasma in 200 patients with OA (NCT03886142).[17] VAS scores showed an improvement of 50% (from a score of 6 to 3) in both groups at 3 months, with values returning to a score of 5 by the sixth month. Scores on the Index of Severity for OA of the Knee were reduced from 7 at baseline to 4 at the third month, increasing to 5 at the sixth month. Twelve month scores were not reported. Platelet-rich plasma is not considered a standard of care treatment for OA and there were a number of additional limitations in conduct and reporting of this study. Limitations of these studies, which include potential for bias due to lack of patient blinding and insufficient number of patients in follow-up.

A single-center, double-blind RCT by Malaithong et al (2022) compared bipolar radiofrequency to a sham RFA procedure using low-level sensory stimulation in 64 individuals with OA (Thailand Clinical Trial Registration 20170130003).[39] Both treatment groups received genicular nerve blocks prior to RFA or sham procedure. The bipolar RFA and sham RFA treatment arms experienced significant improvements in pain at 12 months from baseline, but no differences between groups were observed (Table 6). Similar findings were observed for WOMAC scores

through 12 months follow-up as well as the Patient Global Improvement Index. Interpretation of this study is limited due to the small number of individuals enrolled.

A single-center, double-blind RCT by Ma et al (2024) compared RFA to usual care in patients over 50 years of age with moderate to severe knee OA.[51] A total of 112 patients were randomized. Mean NRS scores were lower among patients in the RFA group at the 6-month follow-up (2.25 vs. 4.53; p<.01) as were worst NRS scores (3.27 vs. 5.42; p<.01). WOMAC scores for pain and physical function were lower in patients receiving RFA; however, stiffness scores were similar between groups.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Participants	Interventions	
				Active	***Comparator***
Davis et al (2018)[8]	U.S.	11	151 patients with chronic (>6 mo) knee pain unresponsive to conservative therapy[a]; pain score ≥6; OA grades 2-4; Oxford Knee Score of ≤35; a positive diagnostic genicular nerve block[a,b]	Cooled RFA of the genicular nerves under fluoroscopic guidance (n=76)	Intra-articular steroid (n=75)
El-Hakeim et al (2018)[9]	Egypt	1	60 patient with stage III or IV knee OA	RFA of the genicular nerves under fluoroscopic guidance (n=30)	Conventional analgesics (n=30)
Xiao et al (2018)[11]	China	1	96 patients with OA with VAS >6 and LKS <60 who had abandoned other therapeutic measures	RFA of the genicular nerves guided by a plexus nerve stimulator (n=49)	Single intra-articular hyaluronic acid injection (n=47)
Chen et al (2020)[15]	U.S.	Multicenter	177 patients with knee OA	Cooled RFA of the genicular nerves under fluoroscopic guidance (n=89)	Single hyaluronic acid injection (Synvisc-One, n=88)
Elawamy et al (2021)[17]	Egypt	2	200 patients with knee OA grade III or IV refractory to conservative management	Pulsed RFA with identification of the genicular nerves based on proximity to the arteries by ultrasound and sensory stimulation (n=100)	Single intra-articular platelet rich plasma (n=100)
Malaithong et al (2022)	Thailand	1	64 individuals with chronic OA grade III or IV refractory to conservative management with a positive diagnostic genicular nerve block[b]	Bipolar RFA of the genicular nerves under fluoroscopic guidance (n=32)	Sham RFA with a genicular nerve block (n=32)
Ma et al (2024)	China	1	112 individuals older than 50 years of age with chronic knee joint pain (grade III or IV and NRS ≥4) for more than 6 months	RFA of the genicular nerves with ultrasound guidance plus nerve block(n=56)	Nerve block (n=56)

LKS: Lysolm Knee Score; OA: osteoarthritis; RCT: randomized controlled trial; RFA: radiofrequency ablation; VAS: visual analog score.
[a] Conservative treatment included physical therapy, oral analgesics: ≤60 mg morphine equivalence, stable for 2 months; intra-articular injections with steroids and/ or viscosupplementation), body mass index (BMI) <40, and reporting ≥50% response to blocks as
[b]At least 50% reduction in numeric rating scale for pain with anesthetic injection to the superomedial and inferomedial branches of the saphenous nerve and the superolateral branch of the femoral nerve.

Table 6. Summary of Key RCT Results

Study	**Mean Pain Scores (SD)**				**Function**	
	1 Month	***3 Months***	***6 Months***	***Responders at 6 Months, %a***	***Mean Oxford Knee Score at 6 Months (SD)***	***Global Perceived Effect at 6 Months, %***
Davis et al (2018)[8]	**NRS**					
N	136	132	126	126	125	126
RFA	3.0 (2.3)	2.8 (2.2)	2.5 (2.3)	74.1	35.7 (8.8)	91.4
Steroid injection	3.9 (2.2)	5.2 (2.0)	5.9 (2.2)	16.2	22.4 (8.5)	23.9
p-Value	.025	<.001	<.001	<.001	<.001	<.001
El-Hakeim et al (2018)[9]	**VAS**			**WOMAC**		
	2 Weeks	***3 Months***	***6 Months***	***2 weeks***	***3 Months***	***6 Months***
N	60	60	60	60	60	
RFA	2.47 (0.3)	2.83 (0.5)	3.13 (0.3)	93.53 (1.9)	21.67 (4.4)	24.23 (4.3)
Analgesics	3.63 (0.27)	4.93 (0.2)	5.73 (0.26)	54.07 (3.0)	30.93 (2.5)	37.1 (1.9)
p-Value	.004	<.001	<.001	.17	.10	<.001
Xiao et al (2018)[11]	**VAS**			**Lysolm Knee Score**		
	3 Days	***6 Months***	***12 Months***	***3 Days***	***6 Months***	***12 Months***
N	96	96	96	96	96	96
RFA	3.38 (1.02	2.41 (1.06)	3.12 (1.03)	78.1 (7.5)	68.3 (6.6)	84.6 (4.3)
Hyaluronic Acid	5.11 (1.13)	5.13 (1.12)	7.01 (1.01)	61.1 (5.3)	54.1 (6.2)	43.2 (6.1)
p-Value	<.05	<.05	<.05	<.05	<.05	<.05
Chen et al (2020)[15]	**NRS**				**WOMAC**	
	1 Month	***6 Months***	***12 Months***	***Responders at 6 Months, %a***	***6 Months***	***12 Months***
N	153	144	128	144	144	128

RFA (95% CI)	3.0 (2.5 to 3.5)	2.7 (2.2 to 3.2)	2.8 (2.2 to 3.4)	71.1%	33.6 (28.4 to 38.9)	33.2 (27.5 to 38.9)
Hyaluronic Acid	NR	NR	NR	NR	NR	NR
Subgroup of control patients who crossed over to RFA at 6 mo	4.2 (3.6 to 4.8)	5.0 (4.4 to 5.6)	3.0 (2.4 to 3.6)	29.4%	58.1 (53.4 to 62.8)	38.4 (32.7 to 44.1)
p-Value	.002	<.001	.618	<.001	<.001	.1996
Elawamy et al (2021)[17]	**VAS**			**ISK**		
	1 Week	***6 Months***	***12 Months***	***1 Week***	***6 Months***	***12 Months***
N	200	NR	NR	200	NR	NR
RFA	3	5	5	5	4	NR
Platelet-rich Plasma	3	5	6	6	6	NR
p-Value	NR	NR	NR	NR	NR	
Malaithong et al (2022)22,	VAS			WOMAC		
	1 Month	6 Months	12 Months	1 Month	6 Months	12 Months
N	64	59	53	64	59	53
RFA	3.0 (2.3)	3.3 (2.7)	3.2 (2.6)	63.6 (51.8)	74.6 (50.3)	67.1 (51.9)
Sham RF	3.1 (1.9)	3.1 (2.3)	2.6 (2.4)	66.8 (42.4)	66.2 (43.5)	24.6 (38.5)
p-Value	.15	.29	.73	.78	.81	.70
Ma et al (2024)	NRS			WOMAC		
	1 Month	3 Months	6 Months	1 Month	3 Months	6 Months
n	110	107	104	110	107	104
RFA + block	2.67 (1.22)	3.18 (1.09)	3.27 (1.06)	34.69 (3.54)	36.09 (3.36)	37.25 (4.35)
Block alone	4.38 (1.16)	4.81 (0.94)	5.42 (1.23)	43.15 (3.84)	43.72 (3.97)	47.86 (4.47)
p-value	<.01	<.01	<.01	<.01	<.01	<.01

CI: confidence interval; ISK: Index of Severity for Osteoarthritis of the Knee; NR: not reported; NRS: numeric rating scale; RCT: randomized controlled trial; RFA: radiofrequency ablation; SD: standard deviation; VAS: visual analog score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Greater than 50% reduction in the NRS.

Table 7. Extended Follow-up of Patients Treated with RFA

Study	Mean Pain Scores (SD)				Function	
	At 12 Months	*At 18 Months*	*At 24 Months*	*Responders at 18 Months, %[a]*	*Oxford Knee Score at 18 Months (SD)*	*Oxford Knee Score at 24 Months (SD)*
Davis et al (2018), Hunter et al (2020)[9,][17,]	NRS					
N (randomized and crossover)	30	25	18	25	25	18
RFA	3.0 (2.5)	3.1 (2.7)	3.6 (2.8)	44.0	47.2 (8.1)	46.8 (10.3)
	At 12 Months	*At 18 Months*	*At 24 Months*	*Responders at 24 Months, %[a]*	*WOMAC Score at 18 Months (SD)*	*WOMAC Score at 24 Months (SD)*
Chen et al (2020), Lyman et al (2022)[18,20,]	NRS					
N (randomized and crossover)	32	32	27	27	32	27
RFA	1.9 (1.9)	2.4 (2.5)	3.4 (3.2)	63.0	34.7 (27.5)	24.8 (32.8)

NRS: numeric rating scale; RFA: radiofrequency ablation; SD: standard deviation;
[a] Greater than 50% reduction in the NRS.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Davis et al (2018)[8,]					
El-Hakeim et al (2018)[9,]	4. Study population was not selected by a positive response to a nerve block		2. Controls received only analgesics and physical therapy if needed		1. Follow-up >6 mo is needed to evaluate durability of the procedure
Xiao et al (2018)[11,]	4. Study population was not selected by a positive response to a nerve block		2. Efficacy of a single injection of hyaluronic acid as an active comparator is not supported by evidence		

Chen et al (2020)[15.]			2.. Efficacy of a single injection of hyaluronic acid as an active comparator is not supported by evidence		
Elawamy et al (2021)[17.]	4. Study population was not selected by a positive response to a nerve block	1. Both groups received analgesics and physical therapy, but these were not recorded.	2. Efficacy of a single injection of platelet-rich plasma as an active comparator is not supported by evidence		
Malaithong et al (2022)		1. Both groups received analgesics therapy, but these were not recorded.			
a et al (2024)	4. Study population was not selected by a positive response to a nerve block				1. Follow-up >6 mo is needed to evaluate durability of the procedure

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Davis et al (2018)[8]		1. Study population was not blinded to treatment assignment, which might have affected subjective scores		1. Unequal loss to follow-up 3. Crossovers to RFA were allowed at 6 mo		
El-Hakeim et al (2018)[9]	2. Allocation concealment not described	1. Study population was not blinded to treatment assignment, which might have affected subjective scores				2. The study did not use a repeated-measures test for the different time points.
Xiao et al (2018)[11]	2. Allocation concealment not described	1. Study population was not blinded to treatment assignment, which might have affected subjective scores			1. Power calculations were not reported	2. The study did not use a repeated-measures test for the different time points.
Chen et al (2020)[15]		1. Study population was not blinded to treatment assignment, which might have affected subjective scores	2. Results were reported only for controls who failed treatment and crossed over			2. The study did not use a repeated-measures test for the different time points.
Elawamy et al (2021)[17]		1. Study population was not blinded to treatment assignment, which might have affected subjective scores		6. It is unclear how many patients completed the 12 month follow- up		2, 4. The study did not use a repeated-measures test and there was no comparison between groups.
Malaithong et al (2022)	2. Allocation concealment not described				4. Power calculations may have underestimated the number of patients needed to recruit; effect size based on older study	

Ma et al (2024)						3. Confidence intervals not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
RFA: radiofrequency ablation.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Nonrandomized Studies

Kapural et al (2022) reported a retrospective assessment of pain relief in 340 consecutive patients with chronic knee pain at a single center who were treated with either C-RFA (n=170) or conventional RFA (n=170) (Table 10).[19] The mean age at treatment was 63 years in the C-RFA group and 61 years in the conventional RFA group; both treatment groups had similar levels of baseline VAS pain reported prior to nerve block (8.4 in the C-RFA group and 8.3 in the traditional RFA group). Included patients had at least one year of follow-up after treatment and were evaluated on short-term and long-term pain outcomes on the VAS and opioid use (Table 11). The authors reported that at the first follow-up, approximately 4 to 6 weeks post-treatment, individuals in the C-RFA group had superior pain reduction on the VAS when compared to traditional RFA as well as significantly longer durability of pain relief. This reduction in pain, however, did not translate into a reduction in the usage of opioids from baseline which showed no significant differences in either treatment arm.

Wu and colleagues (2022) published a retrospective cohort study of C-RFA versus traditional RFA of the genicular nerves in patients who had chronic knee pain despite attempts at conservative management.[40] The mean age of treatment was 72 years of age in the C-RFA group and 69.6 after matching; both groups reported similar levels of baseline NRS pain prior to treatment and similar Kellgren-Lawrence grade for classification of OA. Patients were followed for one year after administration of RFA and were evaluated for treatment success (defined as a reduction of 2 or more on the NRS), duration of pain relief, and the probability of having total knee arthroplasty (TKA) within 1 year post-RFA. In this cohort, patients treated with traditional RFA were significantly more likely to report treatment success at 1, 3 and 6 months follow-up ($p<.01$); the mean duration of relief was 175 days in the c-RFA group and 156 days in the traditional RFA group and did not vary significantly ($p=.69$). The traditional RFA group had a significantly greater reduction in NRS pain scores at 1 month post-RFA (-3.59 versus 4.71; $p=.02$), but this was not sustained at 3, 6, 9 and 12 months follow-up. A higher probability of having TKA was observed in the C-RFA group (14%) compared to traditional RFA (7.7%), but this difference did not reach statistical significance ($p=.18$).

Table 10. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	C-RFA	Traditional RFA	Follow-Up
Kapural et al (2022)	Retrospective	U.S.	2013-2019	340 consecutive individuals with chronic knee pain who had either C-RFA or conventional RFA at a single center. Median VAS pain prior to treatment was 8 prior to nerve block.	C-RFA of the genicular nerves under fluoroscopic guidance following geniculate block (n=170)	Conventional RFA of the genicular nerves under fluoroscopic guidance following geniculate block (n=170)	1 year
Wu et al (2022)	Retrospective	U.S.	NR	208 patients with chronic knee pain who were unresponsive to conservative treatments and had either C-RFA or conventional RFA at a single center. Mean BL NRS pain scores were 7 prior to treatment and the mean Kellgren-Lawrence grade was 3.6.	C-RFA of the genicular nerves (n=104)	Conventional RFA of the genicular nerves (n=104)	1 year

BL: baseline; C-RFA: cooled radiofrequency ablation; NR: not reported; NRS: numeric rating scale; RFA: radiofrequency ablation; VAS: visual analogue scale

Table 11. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	VAS Pain Score Baseline ± SD	VAS Pain Score at 4-6 Wks f/u ± SD	Mean Duration of Pain Relief (≥50% VAS pain decrease)	≥50% VAS Pain Decrease at 6 Mos, n (%)	≥50% VAS Pain Decrease at 12 mos, n (%)	Opioid Usage
Kapural et al (2022)[3,]	340	340	340	340	340	340
C-RFA (n=170)	8.4 ± 1.5	4.26 ± 3.2; p=.001	11.1 mos	107 (63%)	78 (46%)	Mean 53 mg at BL; 53.2 ± 32 mg OME at 12 mos f/u; p=.954
RFA (n=170)	8.3 ± 1.4	5.07 ± 2.8; p=.001	2.6 mos	35 (20.6%)	15 (8.8%)	Mean 48.6mg at BL; 41.5 ± 20 mg OME at 12 mos f/u; p=.054
Diff; p-value	NA	p=.010	8.5 mos; p=0.001	42.6%; NR	37.2%; NR	No between-group comparison

	Treatment Success, % (95% CI) at 1 mo	Treatment Success, % (95% CI) at 3 mo	Treatment Success, % (95% CI) at 6 mo	Mean Change in NRS Pain Score (95% CI) at 3 mo	Mean Change in NRS Pain Score (95% CI) at 6 mo	Mean Change in NRS Pain Score (95% CI) at 12 mo
Wu et al (2022)	104	104	104	104	104	104
C-RFA (n=104)	43 (34 to 53)	55 (45 to 64)	59 (49 to 68)	-1.14 (-2.2 to -0.1)	-0.83 (-2.1 to 0.4)	1 (-2 to 4)
RFA (n=104)	62 (51 to 71)	59 (49 to 68)	79 (70 to 86)	-2.05 (-2.9 to -1.2)	-1.18 (-2.4 to 0.03)	-0.83 (-2.4 to 0.7)
Diff; p-value	.01	<.001	<0.01	.18	.68	.22

BL: baseline; C-RFA: cooled radiofrequency ablation; CI: confidence interval; Diff: difference; f/u: follow-up; mos: months; NR: not reported; NRS: numeric rating scale; OME: oral morphine equivalent; RFA: radiofrequency ablation; SD: standard deviation; VAS: visual analogue scale; wks: weeks.

Coolief Cooled RF System for Pain due to Degenerative Hip Disease

Coolief is a cooled radiofrequency ablation (CRFA) system. It was cleared by the U.S. Food and Drug Administration (FDA) for use in patients with chronic knee pain, but it has not been cleared for treatment of hip pain due to degenerative hip disease. CRFA for chronic hip pain may have promise, in particular because of the larger lesion size it creates, compared with conventional radiofrequency ablation (RFA). Evidence from 3 clinical studies suggests that the Coolief system reduces hip pain to a statistically and clinically significant degree and is associated with minimal complications (Kapural et al., 2018; Kapural et al., 2021; Tran et al., 2022).[33-35] However, the long-term (≥ 6 to 12 months) durability of effect is unclear and only 1 study measured functional outcomes (see Table 12). No systematic reviews or guidelines addressing Coolief by name were identified.

Table 12 Key Outcome Summary

Outcome	Study Findings and Quality
Pain relief	3 very poor-quality pretest-posttest studies reported SS and clinically meaningful pain relief at 6 mos (Kapural et al. 2018; Tran et al., 2022) or 12 mos (Kapural et al., 2021) f/u after Coolief tx and compared w/ BL, although repeat CRFA was performed for some patients.
Opioid use	2 very poor-quality pretest-posttest studies reported no SS differences in opioid use at 6 or 12 mos f/u after Coolief tx compared w/ BL (Kapural et al. 2018; Kapural et al., 2021). 1 very poor-quality pretest-posttest study reported reductions in opioid use at 6 mos f/u after Coolief tx compared w/ BL; however, the outcome was not statistically analyzed (Tran et al., 2022).
Function	1 very poor-quality pretest-posttest study reported SS and clinically meaningful improvement from BL in mean Hip Disability and Osteoarthritis Score (HOOS) at 6 mos f/u after CRFA w/ Coolief (Tran et al., 2022).

AEs	3 very poor-quality pretest-posttest studies reported no or mild self-limiting AEs (Kapural et al., 2018; Kapural et al., 2021; Tran et al., 2022).

Key: AE(s), adverse event(s); BL, baseline; f/u, follow-up; SS, statistically significant(ly); tx, treatment

Safety

In 2021, the Spine Intervention Society's Patient Safety Committee published an article on the safety of genicular nerve RFA.[20] The committee reviewed case reports of septic arthritis, pes anserine tendon injury, third-degree skin burn, and clinically significant hematoma and/or hemarthrosis with RFA of the genicular nerves, concluding that larger cohort studies are needed to determine the incidence of these complications for this emerging technology.

Section Summary: Osteoarthritis (Knee, Hip)

Knee OA is a common disorder in older adults. RFA of the genicular nerves has the potential to alleviate pain and improve function in this population, and might also delay or eliminate the need for TKA. To date, the evidence on RFA for knee pain includes systematic reviews of RCTs, RCTs with 24 to 200 individuals, and prospective observational studies with up to 24 months of follow-up. The systematic reviews generally found that RFA had a benefit on pain, function, and composite scores compared to the control treatments at 3 and 6 month follow-up; however, most estimates were determined to have moderate to high heterogeneity. The network meta-analysis compared multiple RFA modalities and found that cooled RFA had greater efficacy for pain and function through 6 months follow-up than traditional or pulsed RFA. Trials have compared RFA to sham procedures, intra-articular steroid injection, intra-articular hyaluronic acid injection, and platelet-rich plasma injection. Few of the studies were blinded, which may have biased the subjective outcome measures. Additional limitations in design and conduct include suboptimal statistical analyses and reporting of loss to follow-up. The 2 multi-center trials conducted in the U.S. used anesthetic nerve block under fluoroscopic guidance and compared efficacy of cooled RFA to either steroid injection or hyaluronic acid injection. Both studies reported a responder rate above 70% at 6 months which was significantly greater than the control conditions. Given that OA of the knee is a common condition, adequately powered studies preferably blinded studies active and sham controls and follow-up of at least 12 months is needed to determine the benefits and potential harms of this treatment.

Peripheral Nerve Pain

Cryoneurolysis has been proposed as a treatment for peripheral nerve pain; however, there have been a limited number of studies published in the peer-reviewed literature addressing the use of this surgical procedure.

Dasa et al (2016) published a retrospective review of 100 individuals who underwent total knee arthroplasty (TKA) to compare perioperative pain management with and without cryoneurolysis.[45] Cryoneurolysis was performed on the treatment group (n=50) 5 days prior to each TKA as part of a perioperative multimodal pain management program. The control group (n=50) did not receive cryoneurolysis. The results showed a significantly lower number of individuals in the treatment group with a length of stay (LOS) of greater than or equal to 2 days when compared to the control group (6% versus 67%, p<.0001); however, no significant difference between groups was noted for 0 days and 1 day LOS. “The mean ± SE cumulative morphine use during the 12 weeks following surgery was significantly lower for the treatment versus control group (2069.12 ± 132.09 mg vs. 3764.42 ± 287.95 mg, p<.0001)” (Dasa, 2016).

Other evaluated outcomes included mean scores on the Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Oxford Knee Score, 12-item Short Form Health Survey (SF-12), and Patient-reported Outcomes Measurement Information System (PROMIS). Significant reductions in the KOOS from baseline to the 6- and 12-week post-operative visits were noted in the treatment group when compared to the control group (p=.0037 at 6 weeks; p=.0011 at 12 weeks), in the PROMIS pain intensity scores from baseline to 2 weeks post-surgery (p<.0001), and also in the PROMIS pain interference scores from baseline to 6 weeks post-surgery (p<.0001). However, the absolute values of the differences were not reported and there was overlap in the supplemental data. No significant results were noted in other outcomes. No complications were reported due to cryoneurolysis and the most common side effect was local bruising. There were several limitations to this study, including the retrospective, nonrandomized design, and lack of blinding. With the study being single-center and single-surgeon, there is limited generalizability of the results. Furthermore, no disclosure or denial of conflict of interest was reported.

Yoon et al (2016) reported on a prospective study evaluating cryoneurolysis as a treatment for refractory peripheral neuropathic pain.[46] The study was approved for 144 individuals; however, only 28 individuals were screened and 22 were included in the study. All participants were treated with cryoneurolysis for peripheral neuropathy after failure of first- and second-line therapy. Results showed a significant decrease in self-reported pain using a visual analog scale (VAS) at 1 month (p=.0001), 3 months (p=.0002), 6 months (p=.002), and 12 months (p=.03) posttreatment. Cryoneurolysis had to be repeated for 11 (50%) individuals within 12 months of the original treatment. No complications were reported. While this study resulted in positive outcomes, the small sample size and lack of comparator group limits the applicability of the data. In addition, the authors did not disclose the reason for the large gap between the number of individuals approved for the study and the number of individuals screened for the study, which raises concerns for selection bias.

In 2023, Nemecek published a retrospective cohort study of 24 individuals who underwent cryoneurolysis for refractory peripheral mononeuropathy.[47] To be included in the study, individuals needed to have neuropathic pain attributable to a specific peripheral nerve, lack of response to non-invasive therapy, and to experience at least 50% pain relief after two prognostic pain blocks (lidocaine and ropivacaine, respectively). The cohort had a mean pain score of 5.8 (SD, 1.8) before the intervention, using a 10-point numerical rating scale (NRS) to measure pain. Mean NRS scores were 3.4 (SD [standard deviation], 2.6) 1 month after the intervention, 5.4 (SD, 2.1) 3 months after the intervention and 5.5 (SD, 2.0) 6 months after the intervention. Ten participants died before the 3-month follow-up for reasons related to their underlying disease and unrelated to treatment. This study found a short-term benefit associated with treatment, but the benefit dissipated by 3 months. The lack of a control group prevents firm conclusions about the relative effect of cryoneurolysis compared to other pain treatments. The loss of more than 40% of the cohort raises the possibility that results for those lost to follow up, if known, may have significantly affected the results.

Chronic Headaches

Chong et al (2015) reported on a retrospective evaluation on the efficacy and safety of cryoablation for the treatment of occipital neuralgia (ON) in an academic university based pain management center.[48] All patients received local anesthetic injections of ON. Patients with greater than or equal to 50% relief and less than 2 week duration of relief were treated with

cryoablation. Thirty eight patients were included. Of the 38 patients 20 were treated for unilateral greater occipital neuralgia (ON), 10 for unilateral greater and lesser ON, and 8 for bilateral greater ON. There were 10 men and 28 women, with an average age of 45.2 years and 51.1 years respectively. The average relief for all local anesthetic injections was 71.2%, 58.3% for patients who reported 50-74% relief (Group 1) and 82.75% for patients who reported greater than 75% relief (Group 2). The average improvement of pain relief with cryoablation was 57.9% with an average duration of 6.1 months overall. Group 1 reported an average of 45.2% relief for an average of 4.1 months with cryoablation. In comparison, Group 2 reported an average of 70.5% relief for 8.1 months. The percentage of relief (p=.007) and duration of relief (p=.0006) was significantly improved in those reporting at least 75% relief of pain with local anesthetic injections (Group 2 vs. Group 1). Though no significance in improvement from cryoablation was found in men, significance was seen in women with at least 75% benefit with local anesthetic injections in terms of duration (p=0.03) and percentage (p=.001) of pain relief with cryoablation. The average pain score prior to cryoablation was 8 (0-10 visual analog scale, VAS), this improved to 4.2, improvement of 3.8 following cryoablation at 6 months (p=.03). Of the 38 patients, 3 (7.8%) adverse effects were seen. Two patients reported post procedure neuritis and one was monitored for procedure related hematoma. Study limitations included the retrospective nature of the study. Additionally, only the percentage relief, pain score and duration of relief were collected. This study was limited by design and lack of long term outcomes.

Stogicza et al (2019) described an ultrasound (US) guided cryoneuroablation technique of the proximal greater occipital nerve (GON).[49] The authors provide a description of the procedure based on experience in the authors' clinic. With the patient in the prone position, the US probe is placed parallel to the inferior oblique capitis muscle (IOCM). The GON is seen on top of the IOCM; a midline 2-mm incision allows access to the bilateral GONs with a single skin entry. Using an in-plane approach, the cryo probe is advanced to the nerve in a medial-to-lateral direction, with constant US visualization, staying far away from the spinal cord and vertebral artery, which increases safety. The authors concluded that based on anecdotal evidence, cryoneuroablation of the GON can be performed safely, however a formal study is warranted.

Grigsby et al (2021) recently published the results of a pilot study evaluating the safety and efficacy of percutaneous cryoneurolysis for the treatment of occipital neuralgia (ON) related pain. [50] A total of 26 patients (mean age 49.1 years) participated in this prospective, multicenter, nonrandomized cohort study which assessed the degree and duration of the effect of cryotherapy for pain reduction in individuals with either unilateral or bilateral ON. Results were measured by assessing level of pain due to ON based on an 11-point numeric scale at baseline and day 7. Ongoing treatment effect was measured at day 30 and day 56 by patient inquiry with “effect”, “no effect” or “no longer effective” as possible responses. Overall, a clinically important improvement of symptoms (≥ 2 points in numeric rating scale) was reported by 64% of participants at day 7, with similar results lasting through day 30. Pain reduction continued for 50% of participants at day 30 and for 35% of participants at day 56. No adverse events were reported. The authors concluded that cryoneurolysis provided substantial relief from pain related to ON ≤ 30 days after treatment with no safety issues, however several limitations to this study were noted. The study was uncontrolled and unblinded in design, so cryoneurolysis was unable to be compared with other ON treatments, and the lack of a control group introduced potential for bias. In addition, the study had a very small population size and did not include outcome measures assessing impact of treatment with cryoneurolysis on quality of life. The researchers recommend more rigorous clinical trials including a larger

population, comparator group(s) and better characterization of participants at baseline to establish efficacy and safety.

Cryoneurolysis for Knee Osteoarthritis or Total Knee Arthroplasty

Clinical Context and Therapy Purpose
The purpose of cryoneurolysis in patients who have OA or TKA is to provide a treatment option that is an alternative to standard therapies. Pain control in individuals with knee OA can delay TKA, while pain control following TKA is essential for patients to participate in physical therapy and promote recovery.

The following **PICO** was used to select literature to inform this review.

Population
The relevant population of interest are patients with OA or who are undergoing TKA.

Interventions
The therapy being considered is percutaneous cryoneurolysis of the anterior femoral cutaneous nerve and/or the infrapatellar branch of the saphenous nerve.

Comparators
The following therapies are currently being used to make decisions about treating OA or TKA: conservative management, which may include corticosteroid injection or oral medications, for OA, and opioid or peripheral nerve blocks with anesthetics, for TKA.

Outcomes
The most clinically relevant outcome measures for pain treatments are measures of pain severity and functional limitations. Pain is most commonly measured with a VAS or NRS. The Oxford Knee Score is scaled between 12 and 60, with 12 representing the best outcome. Quantifiable pre- and posttreatment measures of functional status are also used, such as the 12-Item and 36-Item Short-Form Health Survey. The WOMAC score is also frequently used to evaluate function due to OA. The time for follow-up is within days to determine procedural success and at least 6 months to a year to evaluate durability.

Randomized Controlled Trials
Radnovich et al (2017) reported a double-blind multicenter RCT of cryoneurolysis for patients with mild-to-moderate OA (see Table 13).[21] Compared with sham-treated patients, cryoneurolysis resulted in a greater decrease in WOMAC pain score, WOMAC total score, and VAS score at 30 days (see Table 14). The cryoneurolysis group also had better WOMAC total scores at 90 days but not at 60 days. Improvements in VAS scores did not differ significantly between active and sham treatment groups at 60 and 90 days.

Mihalko et al (2021) reported a non-blinded single-center RCT of cryoneurolysis for individuals with OA planning to undergo TKA.[41] Patients were randomized 1:1 to either cryoneurolysis targeting the superficial genicular nerves or standard of care treatment prior to receiving TKA (Table 12). A significant reduction in the primary outcome of opioid consumption was not reported in the intention to treat (ITT) analysis, but per-protocol (PP) analysis found that patients in the cryoneurolysis group had significantly lower opioid consumption 72 hours, 6 weeks, and 12 weeks post-discharge ($p<.05$) (Table 13). A significant reduction in pain from

baseline was reported at 12 weeks post-discharge but not for earlier evaluated time points when analyzing the PP population. Improvements in the Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) were noted from 72 hours to 12 weeks follow-up in the PP analysis (p<.0001). The authors noted an adverse event rate of 17% in the cryoneurolysis group and 35% in the standard of care comparator.

Table 13. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Radnovich et al (2017)[26]	U.S.	17	2013-2016	180 individuals with mild-to- moderate (grade II-III) knee OA with knee pain ≥40 mm/100-mm VAS and ≥50% reduction in pain on diagnostic block	n=121 percutaneous cryoneurolysis targeting the IBSN with anatomic landmarks (visual and palpation)	n=59 sham cryoneurolysis with a sham tip and local anesthetic
Mihalko et al (2021)	U.S.	1	2017-2019	124 individuals with severe knee OA who were scheduled to under TKA	n=62 cryoneurolysis targeting the superficial genicular nerves (ISN and AFCN) 3 to 7 days prior to TKA	n=62 standard of care prior to TKA

AFCN: anterior femoral cutaneous nerve; IBSN: infrapatellar branch of the saphenous nerve; OA: osteoarthritis; RCT: randomized controlled trial; VAS: visual analog score.

Table 14. Summary of Key RCT Results

Study	Change in WOMAC Score (SEM)				VAS Score (SEM)		
	Pain at 30 Days	***Total at 30 Days***	***At 60 Days***	***At 90 Days***	***At 30 Days***	***At 60 Days***	***At 90 Days***
Radnovich et al (2017)							
N	180	180	180	180	180	180	180
Cryoneurolysis	-16.65 (1.26)	-78.78 (5.81)	-75.75 (5.87)	-80.31 (5.89)	-40.09 (2.87)	-38.53 (2.91)	-37.90 (3.01)
Sham	-9.54 (1.63)	-48.26 (7.51)	-56.28 (7.58)	-56.51 (7.60)	-27.83 (3.68)	-32.44 (3.73)	-31.58 (3.86)
Diff (95% CI)	-7.12 (-11.01 to -3.22)	-30.52(-48.52 to -12.53)	-19.47(-37.64 to -1.30)	-23.80(-42.02 to -5.57)	-12.25(-21.16 to -3.35)	-6.09(-15.11 to 2.94)	-6.32(-15.66 to 3.01)
p	.004	.001	.036[a]	.011			.183
	Opioid consumption	Opioid consumption	Individuals not opioid	Mean		Mean change in	Mean change in

Mihalko et al (2021)	in TDME (SEM) at 6 weeks post discharge, PP	in TDME (SEM) at 12 weeks post discharge, PP	free, n (%) from discharge to 6 weeks, PP	change in NRS (SD) from BL to 6 Weeks, PP	Mean change in NRS (SD) from BL to 12 Weeks, PP	AUC for KOOS JR from BL to 6 weeks, PP	AUC for KOOS JR from BL to 12 weeks, PP
N	48	48	48	48	48	48	48
Cryoneurolysis	4.2 (0.5)	2.4 (0.3)	7 (15%)	2.2 (2.2)	3.2 (2.3)	9.7	16
Standard of care	5.9 (0.6)	3.4 (0.4)	19 (40%)	1.6 (2.0)	2.3 (2)	7.7	14.1
Diff (95% CI)	1.6 (0.1 to 3.2)	1 (0 to 2)	25%	0.6 (-0.2 to 1.5)	0.9 (0 to 1.7)	2	1.9
p	.0186	.0234	.006	.068	.0256	<.0001	<.0001

AUC: are under the curve; BL: baseline; CI: confidence interval; Diff: difference; RCT: randomized controlled trial; SEM: standard error of mean; VAS: visual analog score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Statistical significance was set at a 1-sided level of 0.025.

Tables 15 and 16 display notable limitations identified in the studies evaluated.

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Radnovich et al (2017)[21]	4. A more relevant population would be patients with moderate- to-severe knee osteoarthritis				
Mihalko et al (2021)	3.Baseline level of pain for individuals prior to TKA unclear				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 16. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Radnovich et al (2017)[21]						2. Unclear whether data were modeled for each time point independently or longitudinally
Mihalko et al (2021)				1,2: Almost 25% missing data 6. Per protocol analysis for many outcomes	4. Per protocol analysis below the required	

					number of participants per group in the power calculation	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Nonrandomized Studies

Lung et al (2022) reported a retrospective study of pain relief in 57 individuals with OA and chronic knee pain planning to undergo TKA at a single center who were treated with either cryoneurolysis of the anterior femoral cutaneous nerve (AFCN) or infrapatellar branch of the saphenous nerve (ISN) or conventional TKA without cryoneurolysis.[42] Included patients had at least 1 year of follow-up after treatment and were assessed for the primary outcome of total opioid morphine milligram equivalents (MME) at 6 weeks post-treatment as well as VAS pain, knee injury and osteoarthritis scores (KOOS JR), and short form survey (SF12) outcome measures (Tables 16 and 17). No significant between group differences were found for the outcome of mean total MME during the inpatient stay or follow-up visits at 4 and 6 weeks post-treatment (p>.05). KOOS scores at 12 months follow-up (p=.007) favored the cryoneurolysis group over standard TKA controls, as did SF-12 mental scores (p=.01). However, between-group comparisons on these outcomes at other time points as well as SF12 physician scores and VAS pain at all time points reported, failed to reach significance. Complications were rare and appeared equivalent between groups.

Mont et al (2024) evaluated the Innovations in Genicular Outcomes Registry (iGOR) for outcomes associated with preoperative cryoneurolysis prior to TKA.[52] A total of 80 individuals who had received preoperative cryoneurolysis and 60 who had not were identified from 2021 to 2024. The study is summarized in Tables 17 and 18.

Table 17. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Cryoneurolysis	Control	Follow-Up
Lung et al (2022)	Retrospective	U.S.	2013-2019	57 individuals with OA planning to undergo TKA who had pre-TKA cryoneurolysis of ISN or AFCN nerves compared matched individuals with OA from the same center who received TKA.	Cryoneurolysis delivered by Iovera handheld device of the ISN or AFCN nerves (n=29)	Conventional TKA without cryoneurolysis (n=28)	1 year

Mont et al (2024)	Prospective	U.S.	2021-2024	140 individuals undergoing TKA from the iGOR	Cryoneurolysis delivered by iovera handheld device to the genicular nerves (n=80)	Conventional TKA without cryoneurolysis (n=60)	

AFCN: anterior femoral cutaneous nerve; iGOR: Innovations in Genicular Outcomes Registry; ISN: infrapatellar branch of the saphenous nerve; OA: osteoarthritis; TKA: total knee arthroplasty

Table 18. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	KOOS Score MD BL to 3 mos (SD)	KOOS Score MD BL to 12 mos (SD)	SF12 Physical Score MD BL to 3 mos (SD)	SF12 Physical Score MD BL to 12 mos (SD)	SF12 Mental Score MD BL to 3 mos (SD)	SF12 Mental Score MD BL to 12 mos (SD)
Lung et al (2022)[28]	57	57	57	57	57	57
Cryoneurolysis (n=29)	27.5 (10)	38.8 (11.2)	8.8 (4.3)	12.9 (11.4)	-0.6 (7.8)	3.6 (9.7)
Standard TKA (n=28)	25.7 (22.1)	11.1 (9.6)	2.5 (18.2)	4 (7.8)	3.5 (6.8)	-3.8 (6.2)
Diff; p-value	.4	.007	.1	.2	.2	.2
Mont et al (2024)	Pain Response through 6 mos[a], (%)	Overall Opioid Use through 6 mos (%)	Function Response through 6 mos[b], (%)			
Cryoneurolysis	71.7	31.4	86.6			
Standard TKA	62.2	62.8	87.3			
Diff; p-value	OR: 1.55; 95% CI, 1.15 to 2.07; p=.004	OR: 0.27; 95% CI, 0.19 to 0.38; p<.001	OR: 0.94; 95% CI, 0.62 to 1.41; p=.761			

BL: baseline; Diff: difference; KOOS, Knee Injury and Osteoarthritis Outcome Score; LSM, least squares mean; MD, mean difference; mos: months; NR: not reported; OR: odds ratio; SD: standard deviation; SF: short form; TKA: total knee arthroplasty

[a] Proportion of patients achieving a pre-determined minimal clinically important difference decrease from baseline in pain score.

[b] Proportion of patients achieving a pre-determined minimal clinically important difference in function outcome.

Technical Issues

As noted in a review by Gabriel and Ilfeld (2018), several technical issues have yet to be resolved, including the optimal number of applications for each nerve, the duration of treatment, and the duration of thawing before moving the cannula.[22] The most effective method for determining the location of the probe (e.g., ultrasound or using anatomic landmarks) also needs to be established.

Section Summary: Cryoneurolysis for Knee Osteoarthritis
Two RCTs and 2 nonrandomized studies were identified. One RCT with 180 patients has compared cryoneurolysis with sham treatment in patients who had knee OA. Cryoneurolysis resulted in a greater decrease in WOMAC pain, WOMAC total, and VAS score at 30 days compared with sham-treated controls. Subsequent measurements showed no significant benefit of cryoneurolysis on WOMAC score at 60 days or in VAS scores at 60 or 90 days. Another RCT with 124 individuals compared cryoneurolysis to standard of care treatment for patients with knee OA who were planning to undergo TKA. Cryoneurolysis had a significantly lower rate of opioid consumption, reduction in NRS pain, and KOOS JR performance at 12 weeks from discharge compared to standard of care. A retrospective cohort study reported superiority of cryoneurolysis on the KOOS JR and SF-12 mental score at 1 year follow-up; no significant differences were observed on the SF-12 physical score at 1 year follow-up or on any outcome for 3 month follow-up. A registry study found improved pain and lowered opioid use with cryoneurolysis prior to TKA; however, functional outcomes through 6 months were similar. Several technical issues including the optimal number of applications for each nerve, the duration of treatment, and the duration of thawing before moving the cannula, have yet to be resolved.

Radiofrequency Ablation for Plantar Fasciitis

Clinical Context and Therapy Purpose
The purpose of RFA in patients who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICO** was used to select literature to inform this review.

Population
The relevant population of interest is patients with plantar fasciitis.

Plantar fasciitis is a common cause of foot pain in adults, characterized by deep pain in the plantar aspect of the heel, particularly on arising from bed. While the pain may subside with activity, in some individuals the pain persists and can impede activities of daily living. On physical examination, firm pressure will elicit a tender spot over the medial tubercle of the calcaneus. The exact etiology of plantar fasciitis is unclear, although a repetitive injury is suspected. Heel spurs are a common associated finding, although it has never been proven that heel spurs cause the pain. Asymptomatic heel spurs can be found in up to 10% of the population.
Interventions
The therapy being considered is RFA.

Comparators
The following therapy is currently being used to make decisions about treating plantar fasciitis: conservative management, which may include corticosteroid injection.

Most cases of plantar fasciitis are treated with conservative therapy, including rest or minimization of running and jumping, heel cups, and nonsteroidal anti-inflammatory drugs. Local steroid injection may also be used. Improvement may take up to 1 year in some cases.

Outcomes
The most clinically relevant outcome measures for pain treatments are measures of pain severity and functional limitations. Pain is a subjective, patient-reported measure. Therefore, pain outcomes require quantifiable pre- and posttreatment measures. Pain is most commonly measured using a VAS. Quantifiable pre- and posttreatment measures of functional status are also used, such as the American Orthopedic Foot and Ankle Society (AOFAS) ankle-hindfoot score. The AOFAS ankle-hindfoot scores range from 0 to 100, with up to 40 points for pain, 50 points for functional aspects, and 10 points for alignment. A high score indicates a better outcome. The time for follow-up is within days to determine procedural success and at least 6 months to a year to evaluated durability.

Study Selection Criteria
Because of the variable natural history of plantar fasciitis and the subjective nature of the outcome measures, RCTs are needed to determine whether outcomes are improved with interventions for pain. Trials should include a homogenous population of patients with a defined clinical condition, use standardized outcome measures when possible, and define a priori the clinically significant magnitude of response.

Review of Evidence

Systematic Reviews
A meta-analysis published by Guimaraes et al (2022) reviewed multiple therapeutic interventions to relieve pain from plantar fasciitis.[43] A total of 8 studies of RFA were identified, but only 2 RCTs were included in the pooled analysis of RFA compared to a control group (n=117). The authors performed a dual assessment of the risk of bias of the included studies using the Cochrane Risk of Bias tool and found a low quality of evidence for RFA to relieve pain from plantar fasciitis. The pooled mean difference between groups for pain outcomes was -1.19 (95% CI, -3.54 to 1.15; p=.32), favoring the RFA group, but this estimate did not achieve statistical significance and had a high level of heterogeneity (I^2, 84%).

Randomized Controlled Trials
Two double-blind sham-controlled randomized trials have assessed RFA for the treatment of chronic heel pain (see Table 17). Wu et al (2017) randomized 36 patients to ultrasound-guided pulsed radiofrequency of the posterior tibial nerve.[23] First step pain, average pain, and the AOFAS ankle-hindfoot score were assessed at baseline and at 1, 4, 8, and 12 weeks. Scores at 12 weeks are shown in Table 2. Changes in VAS score in the sham group were modest (<1 on a 10-point VAS) and of short duration (statistically significant at weeks 1 and 4, but not weeks 8 and 12). The AOFAS ankle-hindfoot score was 60.55 at baseline and 60.05 at 12 weeks in the sham group. In the RFA group, VAS scores at weeks 1, 4, 8, and 12 were all significantly lower than baseline (p<.001), and the AOFAS ankle-hindfoot score increased from 55.5 to 87.6 (p<.001). The improvements in pain and function were greater in the RFA group than in the control group (p<.001 for all measures).

Landsman et al (2013) reported on a double-blind randomized crossover trial (N=17) of RFA applied along the medial aspect of the heel.[24] Crossover to the alternative treatment was allowed at 4 weeks. Outcomes assessed weekly were a pain VAS score reported at the first step in the morning, average pain level, and peak pain level (see Table 18). In a graphic presentation of results, patient pain levels for all 3 outcomes decreased after RFA but showed minimal change after sham. After patients crossed over from sham to RFA, there was a steep drop in all pain outcomes. The maximum follow-up assessment was at 16 weeks and appeared to show similar pain levels throughout the follow-up period.

Table 19. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Wu et al (2017)[23]	Taiwan	1	2014-2016	36 patients (40 feet) with recalcitrant plantar fasciitis	Ultrasound-guided pulsed RF stimulation of the posterior tibial nerve	Sham with ultrasound-guided lidocaine injection
Landsman et al (2013)[24]	U.S.	Multicenter	NR	17 patients failed at least 3 prior types of treatments, pain for >3 mo, and VAS score ≥5	RFA procedure, including stimulation of sensory nerves in an awake patient	Sham with all aspects of the RFA procedure, except delivery of RF energy at the final step

NR: not reported; RCT: randomized controlled trial; RF: radiofrequency; RFA: radiofrequency ablation; VAS: visual analog scale.

Table 20. Summary of Key RCT Results

Study	First Step Pain on VAS Score	Average VAS Pain Score		AOFAS Ankle-Hindfoot Score
	At 12 Weeks	*At 12 Weeks*		
Wu et al (2017)[23]				
N	36	36		36
RFA (SD)	1.79 (1.62)	1.54 (1.26)		87.60 (9.12)
Sham (SD)	6.13 (1.75)	6.09 (1.70)		60.05 (11.38)
	Change At 4 Weeks	Change Score	Change in Peak Pain	
Landsman et al (2013)[24]				
N	17	17	17	
RFA	5.0	4.06	5.33	
Sham	1.33	0.8	1.80	
p	.30	.047	.048	

AOFAS: American Orthopedic Foot and Ankle Society; RCT: randomized controlled trial; RFA: radiofrequency ablation; VAS: 10-cm visual analog score.

Tables 21 and 22 display notable limitations identified in each study.

Table 21. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Wu et al (2017)[23]	3. Study did not report a minimum VAS for inclusion criteria				
Landsman et al (2013)[24]		1. Targeted nerve not clearly defined			1. Crossover allowed at 4 wk

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
VAS: visual analog score.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 22. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Wu et al (2017)[23]						
Landsman et al (2013)[24]				3. Crossovers at 4 wk prevented longer-term **assessments**	1. Power calculations not reported	3. Confidence intervals not reported

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Case Series

Kurtoglu et al (2022) reported the largest case series of standard RFA for plantar fasciitis.[44] The retrospective study, conducted in Turkey, included 261 individuals with plantar heel pain for at least 6 months and at least 2 failed conservative treatments. Mean VAS (scale 0-10) was 8 (range 8-9) at baseline and 0 (range 0-7) at the final mean follow-up of 15 months (p<.001). At follow-up, 16 (6.1%) individuals felt the RFA procedure was unsuccessful.

Cozzarelli et al (2010) reported the case series with the longest follow-up.[25] This study reported on a 12-year follow-up of 82 patients who had undergone RFA for heel pain. Patients had undergone RFA between 1994 and 1995 and had been interviewed at 5, 10, and 12 years postprocedure. Baseline pain levels before the procedure were recalled retrospectively at the follow-up interviews. Of 99 patients potentially eligible to be interviewed, the study evaluated 82 patients. The results were presented without statistical testing. It appears that 73 of 82 patients reported being pain-free at 12 years. On a 0-to-10 pain VAS, the pain-free patients rated their pre-procedure pain at a mean of 7.1 and at 0 post-procedure.

Section Summary: Plantar Fasciitis
A meta-analysis found that a pooled assessment of 2 randomized controlled trials (RCTs) investigating radiofrequency ablation (RFA) for pain alleviation in plantar fasciitis did not demonstrate a significant improvement compared to the control group. The analysis revealed significant heterogeneity and the overall quality of evidence was graded as low.
Two randomized, double-blind trials and several case series have shown consistent sensory nerve reductions in pain after RFA for patients with heel pain due to plantar fasciitis. However, several case series had methodologic weaknesses. In two of them, all pain assessments were performed retrospectively, including pretreatment pain assessment. The 2 randomized trials enrolled a few subjects. Due to crossover at 4 weeks in one of the trials, the randomized comparison only evaluated outcomes to 4 weeks. To be more confident in the efficacy of this treatment, studies with larger samples and longer follow-up would be necessary. The safety of the procedure cannot be fully evaluated in the small samples studied so far.

Radiofrequency Ablation or Cryoneurolysis for Occipital Neuralgia and Cervicogenic Headache
The purpose of RFA in individuals who have occipital neuralgia or a cervicogenic headache is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with occipital neuralgia or a cervicogenic headache.

Occipital neuralgia is a specific type of headache that is located on one side of the upper neck, back of the head, and behind the ears, and sometimes extending to the scalp, forehead, and behind the eyes. The pain, which may be piercing, throbbing, or electric-shock-like, follows the course of the greater and lesser occipital nerves. Occipital neuralgia is believed to occur due to pressure or irritation to the occipital nerves, which may result from injury, entrapment by tight muscles, or inflammation.

Cervicogenic headache is a headache that is secondary to a disorder of the cervical spine. The pain may be referred from facet joints, intervertebral discs, or soft tissue. The pain is constant rather than throbbing, and may be aggravated by movements of the neck or pressure to certain areas on the neck. The first 3 cervical spinal nerves can refer pain to the head. The C1 suboccipital nerve innervates the atlanto-occipital joint; the C2 spinal nerve and the C3 dorsal ramus have close proximity to and innervate the C2-C3 facet joint. The C2-3 facet joint is the most frequent source of a cervicogenic headache. A diagnosis of a cervicogenic

headache may be confirmed by an anesthetic block of the lateral atlanto-axial joint, the C2-3 facet joint, or the C3-4 facet joint.

Interventions
The therapy being considered is RFA or cryoneurolysis. These treatments involve the percutaneous insertion of a catheter that is directed toward the nerve of interest, and are used to ablate the nerve by thermal lesioning.

Comparators
Treatment for occipital neuralgia may include massage and rest, muscle relaxants, nerve blocks, and injection of steroids directly into the affected area.

Treatment for cervicogenic headache may include nerve blocks, physical therapy, and exercise.

Outcomes
The most clinically relevant outcome measures for pain treatments are measures of pain severity and functional limitations. Pain is most commonly measured with a VAS or RNS. Quantifiable pre- and posttreatment measures of functional status are also used, such as the 12-Item and 36-Item Short-Form Health Survey. The time for follow-up is within days to determine the procedural success and months to years to evaluate durability.

Systematic Reviews
Grandhi et al (2018) conducted a systematic review of RFA for the treatment of a cervicogenic headache.[27] Ten studies met selection criteria, including 3 RCTs, 3 prospective studies, and 4 retrospective studies. There were no high-quality RCTs. Two of the RCTs evaluated RFA of the facet joints and failed to find a benefit of RFA. The third RCT compared RFA with steroid injection of the greater occipital nerve, finding no difference between the groups in the short term, but a longer duration of pain control in the RFA group.

A systematic review by Ducic et al (2014) did not identify any RCTs assessing RFA for chronic occipital neuralgia.[28] Reviewers identified 3 case series (total n=131 patients) on pulsed RF treatment. Success rates in these series ranged from 51% to 100%, with an overall success rate of 55%. Follow-up ranged from 3 to 10 months.

Randomized Controlled Trials
A double-blinded RCT of 52 patients who were treated with cryoneurolysis or injection of corticosteroid and local anesthetic in a tertiary pain clinic was reported by Kvarstein et al (2019).[29] The investigators noted a temporary benefit of both treatments for cervicogenic headache, but there was no additional benefit for the more invasive procedure. A possibility of adverse effects of repeated occipital cryoneurolysis were noted to include scar and neuroma formation and a risk of neuropathic pain.

Section Summary: Radiofrequency Ablation for Occipital Neuralgia and Cervicogenic Headache
No RCTs of RFA for chronic occipital neuralgia have been identified. A systematic review identified 3 RCTS of RFA for a cervicogenic headache, none of which were high quality. Pain is a subjective, patient-reported measure that is particularly susceptible to a placebo effect. Trials with sham or active controls are needed to evaluate the efficacy of this treatment.

One RCT that compared cryoneurolysis with injection of corticosteroid and local anesthetic found no significant improvement with the more invasive treatment.

SUMMARY OF EVIDENCE

For individuals who have knee or hip osteoarthritis (OA) who receive radiofrequency ablation (RFA) of the peripheral nerves, the evidence includes systematic reviews of randomized controlled trials (RCTs), RCTs with 24 to 200 individuals, and non-randomized comparative studies with up to 12 months of follow-up. Relevant outcomes include symptoms, functional outcomes, and quality of life (QOL). Knee OA is a common disorder in older adults. RFA of the genicular nerves has the potential to alleviate pain and improve function in this population, and this therapy might also delay or eliminate the need for TKA. At this time, there is high heterogeneity in methods and comparators. The systematic reviews generally found that RFA had a benefit on pain, function, and composite scores compared to the control treatments at 3 and 6-month follow-up; however, most estimates were determined to have moderate to high heterogeneity. The network meta-analysis compared multiple RFA modalities and found that cooled RFA had significantly improved efficacy for pain and function through 6 months follow-up compared with traditional or pulsed RFA. The 2 multicenter trials conducted in the U.S. used anesthetic nerve block under fluoroscopic guidance and compared efficacy of cooled RFA to either steroid injection or hyaluronic acid injection. Both studies reported a responder rate of approximately 70% at 6 months, which was significantly greater than the control conditions. A small, double-blind RCT of bipolar RFA with genicular nerve block compared to genicular nerve block and sham RFA found no differences between groups for visual analog score (VAS) pain or the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores through12 months follow-up. Given that OA of the knee is a common condition; adequately powered studies, preferably blinded with active and sham controls and follow-up of at least 12 months, is needed to determine the benefits and potential harms of this treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have knee osteoarthritis (OA) or total knee arthroplasty (TKA) who receive cryoneurolysis of peripheral nerves, the evidence includes 2 RCTs with a total of 304 participants, a comparative, retrospective cohort study of 57 participants, and a registry study of 140 individuals. Relevant outcomes include symptoms, functional outcomes, and QOL. In one RCT, cryoneurolysis in individuals with knee OA resulted in a greater decrease in WOMAC pain score, WOMAC total score, and VAS score at 30 days compared with sham-treated controls. However, subsequent measurements showed no significant benefit of cryoneurolysis on WOMAC score at 60 days or VAS scores at 60 or 90 days. Another RCT investigated cryoneurolysis compared to standard of care for patients with knee OA who were planning to undergo TKA. Cryoneurolysis resulted in a lower rate of opioid consumption, a reduction in numeric rating scale (NRS) pain scores, and Knee injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) functional performance at 12 weeks post discharge. The retrospective cohort study reported superiority of cryoneurolysis on the KOOS JR and Short Form-12 item (SF-12) mental score at 1 year follow-up; no significant differences were observed on the SF-12 physical score at 1 year follow-up or for any outcome at earlier 3 month assessment. A registry study found improved pain and lowered opioid use with cryoneurolysis prior to TKA; however, functional outcomes through 6 months were similar. Several technical issues including the optimal number of applications for each nerve, the duration of treatment, and the duration of thawing before moving the cannula have not been resolved. The most effective method for determining probe insertion location (e.g., ultrasound-

guided or based on anatomic landmarks) also need to be established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have plantar fasciitis who receive radiofrequency ablation of the peripheral nerves, the evidence includes two RCTs and a meta-analysis. Relevant outcomes include symptoms, functional outcomes, and QOL. The meta-analysis pooled evidence from 2 RCTs and did not demonstrate a significant improvement in pain outcomes compared to the control group. The analysis revealed significant heterogeneity, and the overall quality of evidence was graded as low. One of the randomized trials only evaluated 17 patients, and assessment of randomized outcomes was limited to 4 weeks post-treatment. A second RCT evaluated 36 patients out to 12 weeks. The case series generally had small sample sizes, and many had methodologic deficiencies such as retrospective assessment of pain. To be more confident in the efficacy of this treatment, controlled trials with larger samples and longer follow-up would be necessary. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have occipital neuralgia or cervicogenic headache who receive RFA or cryoneurolysis of peripheral nerves, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, and QOL. No RCTs of RFA for chronic occipital neuralgia have been identified. Three RCTs of RFA for a cervicogenic headache have been published, none of which were high quality. Pain is a subjective, patient-reported measure that is particularly susceptible to a placebo effect. Randomized trials with sham or active-controls are needed to evaluate the efficacy of this treatment. One controlled trial found a temporary benefit of cryoneurolysis for cervicogenic headache, but the effect was not significantly better than injection of corticosteroid and local anesthetic. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who suffer with chronic headaches the evidence is limited to a retrospective study. No randomized controlled trials were found. The evidence is insufficient to establish the safety and efficacy of this technique in the treatment of pain associated with occipital neuralgia and/or chronic headaches (including but not limited to cervicogenic headache, migraines, cluster headaches, tension headaches). Further larger well-designed studies with longer periods of follow-up are needed to evaluate the use of cryoneurolysis (cryoablation, cryotherapy or cryoanalgesia) for these conditions and to identify which patients would benefit from this procedure. The evidence is insufficient to determine the effects of this technology on net health outcomes.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 23.

Table 23. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05286996	Cryoneurolysis for TKA - a Pilot Study	20	Oct 2023

NCT05591768	Monopolar Versus Bipolar Radiofrequency in OA Knee Pain	70	Mar 2024
NCT05700253	Comparing Pain Outcomes of Treatment Strategies for Osteoarthritis Knee Patients	76	Sep 2024
NCT05920382	Radiofrequency Ablation for the Treatment of Post-knee Arthroplasty Chronic Pain	86	Dec 2027
NCT02915120	Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo-Controlled Trial	142	Jul 2024
NCT06173830	Comparison of the Effectiveness of Physical Therapy With Ultrasound-Guided Radiofrequency Ablation of the Genicular Nerve in Patients With Chronic Knee Osteoarthritis	68	Apr 2024
NCT06094660	Patients With Knee Pain Caused by Osteoarthritis: Comparison of Conservative Medical Management With RadioFrequency Ablation or Chemical Neurolysis of the Genicular Nerves With Phenol	192	Nov 2026
Unpublished			
NCT02294864	A Controlled Comparison of Pulsed Radiofrequency Vs Physical Therapy on Treating Chronic Knee Osteoarthritis	50	Apr 2017 (unknown)
NCT02260869	Efficacy of Cooled and Monopolar Radiofrequency Ablation of the Geniculate Nerves for the Treatment of Chronic Osteoarthritic Knee Pain	78	Jun 2019 (terminated due to finances)
NCT03818022	Effectiveness of Preoperative Cryoneurolysis (Iovera) for Postoperative Pain Control in Total Knee Arthroplasty	100	Dec 2020 (study withdrawn)
NCT04145011[a]	A Prospective, Multi-center, Randomized, Single Blind Clinical Trial Comparing COOLIEF* Cooled Radiofrequency to Conventional Radiofrequency Ablation of the Genicular Nerves in the Management of Knee Pain in an Osteoarthritic Patient Population	153	Oct 2022

NCT: national clinical trial
[a] Denotes manufacturer sponsored or cosponsored trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Orthopedic Surgeons et al
In 2021, the American Academy of Orthopaedic Surgeons published a clinical practice guideline, endorsed by the American Association of Hip and Knee Surgeons and the American Physical Therapy Association, on management of osteoarthritis (OA) of the knee. [16,] The guideline did not specifically address RFA or cryoneurolysis, but did include a guideline statement on denervation therapy that included various ablation techniques (e.g., RFA, cryoneurolysis, thermal ablation and chemical ablation). The guideline stated, "denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee" (strength of recommendation: limited).

American College of Rheumatology and Arthritis Foundation
2019 Guidelines from the American College of Rheumatology and the Arthritis Foundation gave a conditional recommendation for radiofrequency ablation for the treatment of knee osteoarthritis.[30,] The recommendation was based on evidence of a potential analgesic benefit, but the studies used heterogeneous techniques and there was a lack of long- term safety data.

American College of Foot and Ankle Surgeons (ACFAS)
The American College of Foot and Ankle Surgeons (2018) issued consensus guidelines on the diagnosis and treatment of acquired infracalcaneal heel pain.[31,] The safety and efficacy of bipolar radiofrequency were listed as uncertain (neither appropriate nor inappropriate).

American Society of Pain and Neuroscience
The American Society of Pain and Neuroscience (2021) issued consensus guidelines using U.S. Preventive Services Task Force (USPSTF) grading criteria on the use of RFA to treat various pain conditions.[26] The guidelines stated that genicular RFA may be used for the treatment of osteoarthritis-related and post-surgical knee joint pain (Grade B), and may be selectively offered for the treatment of occipital neuralgia pain when greater or lesser nerves have been identified as the etiology of pain via diagnostic blocks (Grade C).

U.S. Preventive Services Task Force Recommendations
Not applicable.

Government Regulations

National
No NCD available for this service.

Local
No LCD available for this service.

Noridian: Billing and Coding: Cryoneurolysis Instruction A59752, effective date: 1/1/24
CMS National Coverage Policy
N/A

Article Guidance

Article Text
CRYONEurolysis a medical treatment which has been proposed to be a mechanism for relieving pain by freezing the affected peripheral nerves.

One manufacturer of this system, Iovera, instructs providers on their website to bill the treatment with Current Procedural Terminology (CPT) 64640 (Destruction by neurolytic agent; other peripheral nerve or branch) or CPT code 64624 (Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed). Codes 64640 and 64624 require the destruction of target nerve(s). The Iovera system is temporary and not destructive. Therefore, CPT codes 64640 and 64624 are not appropriate for Medicare billing.

While there is no specific CPT code for cryoneurolysis, Noridian has determined the most appropriate codes for this technology are represented by codes 0440T, 0441T and 0442T, until a permanent CPT code is provided.

0440T - Ablation, percutaneous, cryoablation, including image guidance; upper extremity distal/peripheral nerve
0441T - Ablation, percutaneous, cryoablation, including image guidance; lower extremity distal/peripheral nerve
0442T - Ablation, percutaneous, cryoablation, including image guidance; nerve plexus or truncal nerve (e.g. Brachial plexus, pudendal nerve)
Use 0441T for the Iovera system for use in the knee.

Note: Noridian may request additional documentation and review on case-to-case basis for medical necessity.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

1. Radiofrequency Ablation of Primary or Metastatic Liver Tumors
2. Spinal Surgery: Percutaneous Intradiscal Electrothermal (IDET) Annuloplasty and Percutaneous Intradiscal Radiofrequency Annuloplasty, and Biacuplasty
3. Spinal Surgery: Percutaneous Disc Decompression Using Laser Energy or Radiofrequency Ablation (Nucleoplasty)
4. Facet Joint Denervation

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57. HAYES Technology Assessment -Cooled Radiofrequency Ablation with the Coolief Cooled RF (Avanos Medical Inc.) System for Osteoarthritis of the Knee, Feb 21, 2020, Annual Review: May 2, 2023

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 9, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/18	4/17/18	4/17/18	Joint policy established
7/1/19	4/16/19		Added Occipital Neuralgia and Cervicogenic Headache to MPS as E/I. Updated rationale, added reference 7 & 8.
7/1/20	4/14/20		Routine policy maintenance. Updated rationale section, added references. No change in policy status.
11/1/20	8/18/20		Added code 64625 as E/I. No changes in policy status.
11/1/21	8/17/21		Routine policy maintenance. No change in policy status.
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		Routine maintenance Added paragraph and Table 12 for Coolief Cooled RF System for Pain due to Degenerative Hip Disease under Rationale Vendor: N/A (ky)
11/1/24	8/20/24		Routine maintenance No change in status References added Vendor: TP (ky)
1/1/25	10/15/24		Routine maintenance No change in status References added This policy was previously titled: “Radiofrequency Ablation of Peripheral Nerves to Treat Pain including Coolief Cooled RF”. The topic was combined with JUMP policy, “Cryoablation or

			Cryoneurolysis (e.g., iovera° System) of Peripheral Nerves". The policy title is updated to, "Ablation of Peripheral Nerves to Treat Pain including Coolief Cooled RF and Iovera System". Vendor: TP (ky) Post JUMP changes/comments: Removed including Coolief Cooled RF in the below MPS statement: o Radiofrequency ablation of peripheral nerves to treat pain (e.g., plantar fasciitis, occipital neuralgia, cervicogenic headache, osteoarthritis, etc.) is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes. Combined the below MPS into one statement: o Cryoneurolysis of peripheral nerves to treat pain associated with knee osteoarthritis, cervicogenic headache, or total knee arthroplasty is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes. (ky)

Next Review Date: 4th Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ABLATION OF PERIPHERAL NERVES TO TREAT PAIN INCLUDING COOLIEF COOLED RF AND IOVERA SYSTEM

- **Coverage Determination:**

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Not covered

- **Administrative Guidelines:**

N/A