Research Article

Thermal Nerve Radiofrequency Ablation for the Nonsurgical Treatment of Knee Osteoarthritis: A Systematic Literature Review

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ABSTRACT

Background: There are roughly 14 million adults in the United States presenting with symptomatic osteoarthritis (OA) of the knee. Nerve radiofrequency ablation (RFA) is a nonsurgical procedure for the management of knee OA symptoms, and no previous systematic review has been performed comparing geniculate nerve RFA to other nonsurgical treatments.

Questions/Purposes: (1) How does geniculate nerve RFA compare with other nonsurgical modalities for patients with knee OA about pain, function, quality of life, and composite scores? and (2) How does geniculate nerve RFA compare with other nonsurgical modalities for patients with knee OA about adverse events (AEs)?

Methods: A systematic literature review was conducted within PubMed, EMBASE, and Cochrane Central Register of Controlled Trials to identify all studies from 1966 to 2019 evaluating the relative effectiveness of geniculate nerve thermal (heated or cooled) RFA compared with other nonsurgical treatments for knee OA. Two independent abstractors reviewed and analyzed the literature including comparators such as intra-articular (IA) corticosteroids, IA hyaluronic acid, NSAIDs, acetaminophen (paracetamol), and control/sham procedures. Inclusion was based on the following criteria: English language, human subjects, symptomatic knee OA, and patient-reported outcomes.

Results: Five high-quality and two moderate-quality randomized controlled trials (RCTs) met the inclusion criteria for this review. The results showed consistent agreement across all RCTs in favor of geniculate nerve thermal RFA use for nonsurgical treatment of knee OA. One high-quality RCT and one moderate-quality RCT found geniculate nerve RFA to provide statistically significant outcome improvement compared with control or sham procedures regarding pain, function, quality of life, and composite scores. When compared

with IA corticosteroids and hyaluronic acid, geniculate nerve RFA also provided notable improvement in pain, function, and composite scores (visual analog scale, Western Ontario, and McMaster Universities Arthritis Index, and Oxford Knee Score). RFA was markedly favored for all pain and composite outcomes (Western Ontario and McMaster Universities Arthritis Index and visual analog scale). The included RCTs did not report any serious AEs related to geniculate nerve RFA.

Discussion: These results demonstrate geniculate nerve thermal RFA to be a superior nonsurgical treatment of knee OA compared with NSAIDs and IA corticosteroid injections. None of the RCTs reported any serious AEs with geniculate nerve thermal RFA, as opposed to known cardiovascular, gastrointestinal, and renal AEs for NSAIDs and accelerated cartilage loss and periprosthetic infection risk for IA corticosteroid injections.

Level of Evidence: Level I

The societal impact of knee osteoarthritis (OA) is notable. The lifetime risk of developing symptomatic knee OA is estimated to be 45%.[1] With changing demographics and an increasing percentage of the United States cohort older than 65 years of age, the burden of knee OA will increase.[2,3] Although a single randomized controlled trial (RCT) demonstrated that total knee arthroplasty (TKA) was more effective than nonsurgical treatment of end-stage knee OA,[4] effective nonsurgical treatments are necessary to manage different subgroups of patients with knee OA including patients who have (1) mild/moderate knee OA, (2) are poor surgical candidates, or (3) decline TKA surgery (approximately 20% of patients are not satisfied with their TKA).[5-7]

The American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee, Second Edition* evidence-based clinical practice guideline (CPG) recommends (1) self-managed strengthening and/or low-impact aerobic exercise programs (strong evidence), and NSAIDs (strong evidence), and (3) weight loss in patients with a body mass index $\geq$ 25 kg/m^2 (moderate evidence).[8] Intra-articular (IA) hyaluronic acid (HA) injections are not recommended. IA HA did not provide clinically notable pain improvement (strong evidence). The HA recommendation is supported by three independent meta-analyses[9-11] and a network meta-analysis.[12]

The evidence for IA corticosteroid injections was inconclusive in the AAOS CPG. However, a subsequent network meta-analysis[12] shows IA corticosteroids are the most effective treatment of knee OA pain for 4 to 6 weeks, naproxen (an NSAID) is the most effective treatment of knee OA function for 4 to 6 weeks, and naproxen is the most effective treatment of combined knee OA pain and function. Based on the same study, knee corticosteroid injections have not been shown to be effective beyond 6 weeks.

Although adverse events (AEs) and contraindications are considered, the focus for many AAOS CPG recommendations is treatment effectiveness. Of the four knee OA effective treatments discussed above, NSAIDs and IA corticosteroid injections have notable adverse effects and/or contraindications. The FDA issued a "black box" warning on all NSAIDs because of increased cardiovascular risk associated with NSAID use,[13] and a meta-analysis by Varas-Lorenzo et al[14] described the varying levels of individual cardiovascular risks for each NSAID. NSAIDs are also associated with gastrointestinal complications[15] and renal toxicity,[16] whereas IA corticosteroid injections are associated with accelerated OA progression[17,18] and increased risk of periprosthetic joint infection if knee arthroplasty surgery is subsequently performed within 3 to 6 months of the injection.[19,20] A recent AAOS symposium, "Optimizing Clinical Use of Biologics in Orthopaedic Surgery," highlighted the need for additional nonsurgical treatments for knee OA. "The clinical use of biologics such as platelet-rich plasma and cell-based therapies to treat orthopaedic [conditions] has greatly outpaced the evidence. This phenomenon is . . . in part due to the lack of satisfactory conventional treatment options, . . .[21]"

Thermal radiofrequency ablation (RFA) is the application of heat to ablate the superior lateral, superior medial, and inferior medial genicular sensory nerve branches around the knee to reduce the pain associated with OA.[22] Multiple RCTs have been conducted on the application of thermal RFA to treat knee OA. However, no systematic review has quantitatively compared geniculate nerve thermal RFA to other effective nonsurgical treatments of knee OA. Thus, the purposes of this study were to (1) determine how geniculate nerve RFA compares with other nonsurgical modalities for patients with knee OA about pain, function, quality of life, and composite scores and (2) evaluate how

Figure 1

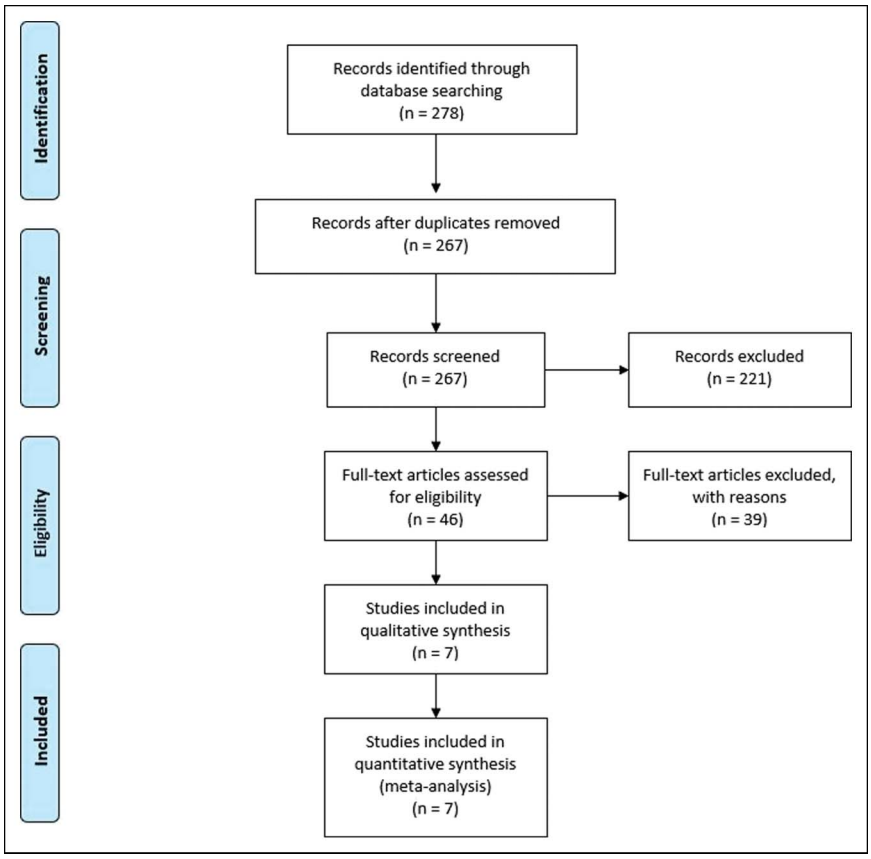

Chart showing the literature search flowchart.

geniculate nerve RFA compares with other nonsurgical modalities for patients with knee OA about AEs.

Methods

A comprehensive search of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted based on the key terms and concepts to identify all studies evaluating the relative effectiveness of geniculate nerve thermal (heated or cooled) RFA compared with other nonsurgical treatments of knee OA. Bibliographies of relevant systematic reviews were manually searched for additional references. All databases were last searched on November 13, 2019, with the limits for publication dates from 1966 to present and English language. Full search strategy can be found in the Supplemental Data File (Supplemental Digital Content 1, http://links.lww.com/JAAOS/A517).

Two independent abstractors (F.C. and V.V.) reviewed and analyzed the literature for geniculate nerve thermal RFA including comparators such as: IA corticosteroids, IA HA, oral analgesics, and control/sham procedures. Geniculate nerve thermal RFA is often performed by a preprocedural anesthetic block with monitoring of pain relief, followed by nerve ablation using probes inserted under fluoroscopy or ultrasonography guidance using anatomic landmarks. Inclusion was based on the following criteria: English language, human subjects, symptomatic knee OA, comparative design, and quantitative patient-reported outcome data. As shown in Figure 1, of the 267 unique abstracts returned from the systematic search, 46 full-text articles were reviewed and seven randomized trials met the inclusion criteria for analysis.[23] The quality of included articles was appraised based on the GRADE methodology assessing possible risk of bias in the following domains: randomization, allocation concealment, blinding, incomplete data, selective reporting, and other bias (relevant author conflict, industry funding, baseline differences, or unaccounted confounding factors).[24] Unusual methodology and quality appraisal disagreements between abstractors were individually assessed and consensus was reached.

Clinical effectiveness of pain relief was determined as pain relief greater than or equal to the minimum clinically

Table 1. Summary of Significant Patient Outcomes by Nonsurgical Treatment Comparison

Comparison Groups	Outcome Measure	Favored Treatment
Radiofrequency ablation (RFA) versus IA corticosteroids		
Davis et al[26]	Pain	Cooled RFA
	Function	Cooled RFA
Sari et al[31]	Pain	RFA
	Function	RFA
	Stiffness	RFA
	Composite	RFA
RFA versus IA HA		
Ray et al[32]	Pain	RFA
	Composite	RFA
Xiao et al[28]	Pain	RFA
	Function	RFA
RFA versus acetaminophen/diclofenac		
El-Hakeim et al[27]	Pain	RFA
	Function	RFA
	Stiffness	Acetaminophen/diclofenac
	Composite	RFA
RFA versus sham/control		
Choi et al[29]	Pain	RFA
	Function	RFA
	Composite	RFA
Shen et al[30]	Pain	RFA
	Function	RFA
	Composite	RFA

HA = hyaluronic acid, IA = intra-articular

important difference (MCID) or minimal clinically important improvement. The MCID for pain relief was 1.99[25] and was the same MCID used in the AAOS *Treatment of Osteoarthritis of the Knee, Second Edition* evidence-based CPG.

Included study group means and standard deviations were extracted for all pain, function, and composite patient-reported outcomes, including visual analog scale, numeric rating scale, Western Ontario, and McMaster Universities Arthritis Index (WOMAC), Short Form-36, Lysholm knee score, Oxford Knee Score, and Global Perceived Effect (GPE). These values were then used to calculate the mean difference, and statistical significance was evaluated using a 95% confidence interval. Meta-analysis was assessed using STATA 12.1 software, but the level of heterogeneity was too high for reliable comparison because of varying treatment and outcome comparisons.

Results

Search Results

Five high-quality and two moderate-quality RCTs met the inclusion criteria for this systematic review.[26-32] Regarding the primary outcomes, all included studies reported pain and six of seven studies reported functional outcomes (Table 1). Composite scores built from pain, function, stiffness, and other patient-reported outcomes were also collected and reported (Table 1). The most common follow-up time was three months. However, three studies assessed outcomes

Figure 2

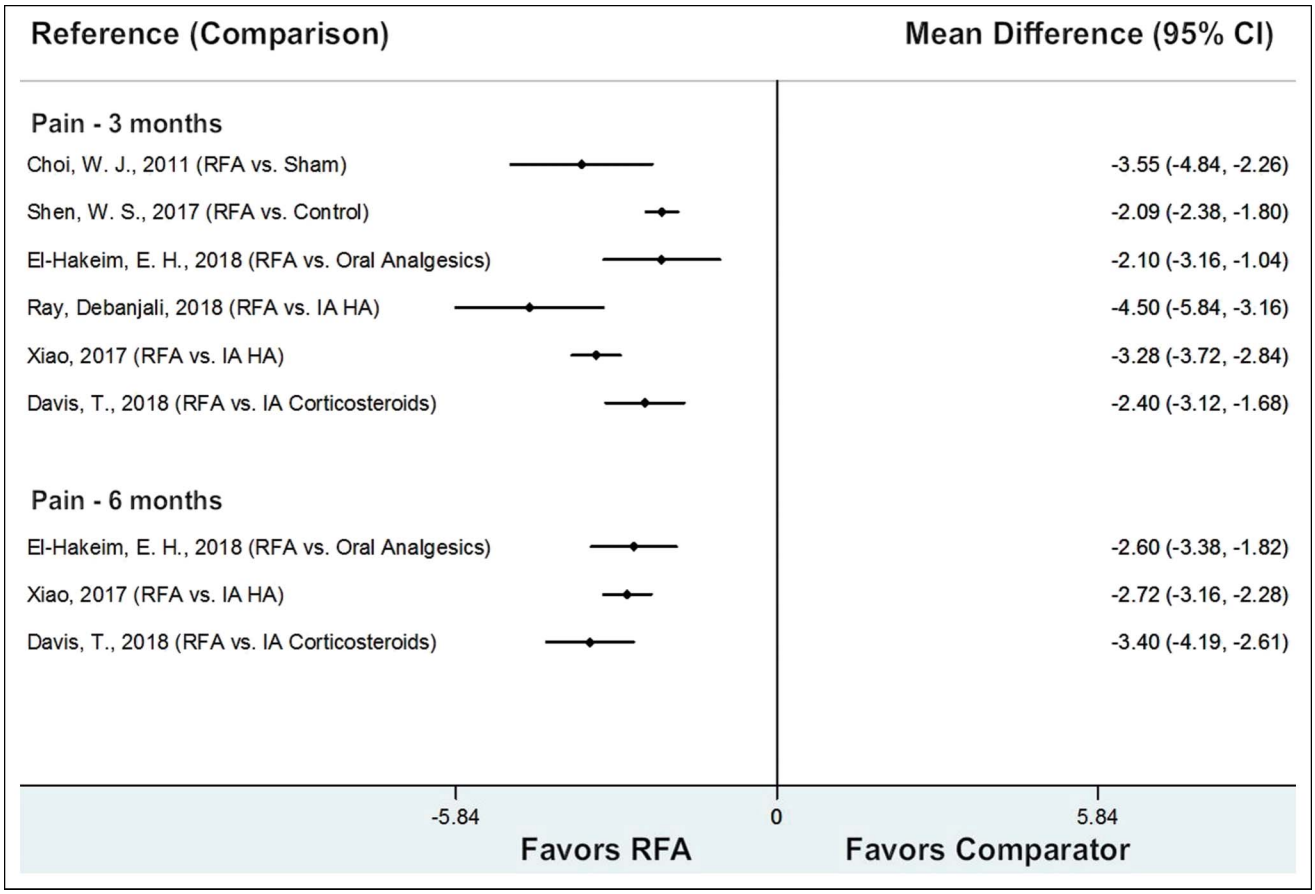

Chart showing pain outcomes of radiofrequency ablation (RFA) treatment comparisons. CI = confidence interval, HA = hyaluronic acid, IA = intra-articular

at six months[26-28] and one study[27] measured outcomes up to 1 year.

Patient Outcomes

Overall, the results showed agreement across studies in favor of geniculate nerve thermal RFA use for conservative treatment of knee OA for nearly all measured outcomes and treatment comparisons. One high-quality[29] and one moderate-quality[30] RCT compared geniculate nerve RFA with sham/control procedures and found geniculate nerve RFA to be markedly superior for pain and functional outcomes (Figures 2 and 3). Geniculate nerve RFA also displayed superiority over a variety of active treatment comparisons within the included studies. When compared with IA corticosteroids, one high-quality RCT[31] found that geniculate nerve heated RFA was markedly favored for WOMAC function ($P = 0.003$ at 1 month) and stiffness ($P = 0.007$ at 3 months) and visual analog scale pain ($P = 0.001$ at 1 month), although no significant difference was noted on the WOMAC pain subscale ($P = 0.639$). Another high-quality RCT[26] evaluated geniculate nerve cooled RFA to IA corticosteroids and found RFA to be markedly favored for reducing pain and improving function (Figures 2 and 3) measured up to 6 months after intervention. When geniculate nerve RFA was compared with acetaminophen and diclofenac, one high-quality RCT[27] showed geniculate nerve RFA to provide notable benefit for overall WOMAC, function, and pain for up to 6 months (Figures 2 and 4). However, for the subset outcome of stiffness, the acetaminophen/diclofenac combination appeared to provide a notable improvement over geniculate nerve RFA at 3 ($P = 0.004$) and 6 months ($P < 0.001$).[27] One high-quality[32] and one moderate-quality[28] RCT compared geniculate nerve RFA with IA HA. Both studies found geniculate nerve RFA to be markedly superior to IA HA for pain, function, and composite outcomes (Figures 2–4); the moderate-quality RCT measured pain and function as far as 1 year.[28]

The composite outcome scores of WOMAC, Short Form-36, and GPE were used for geniculate nerve RFA

Figure 3

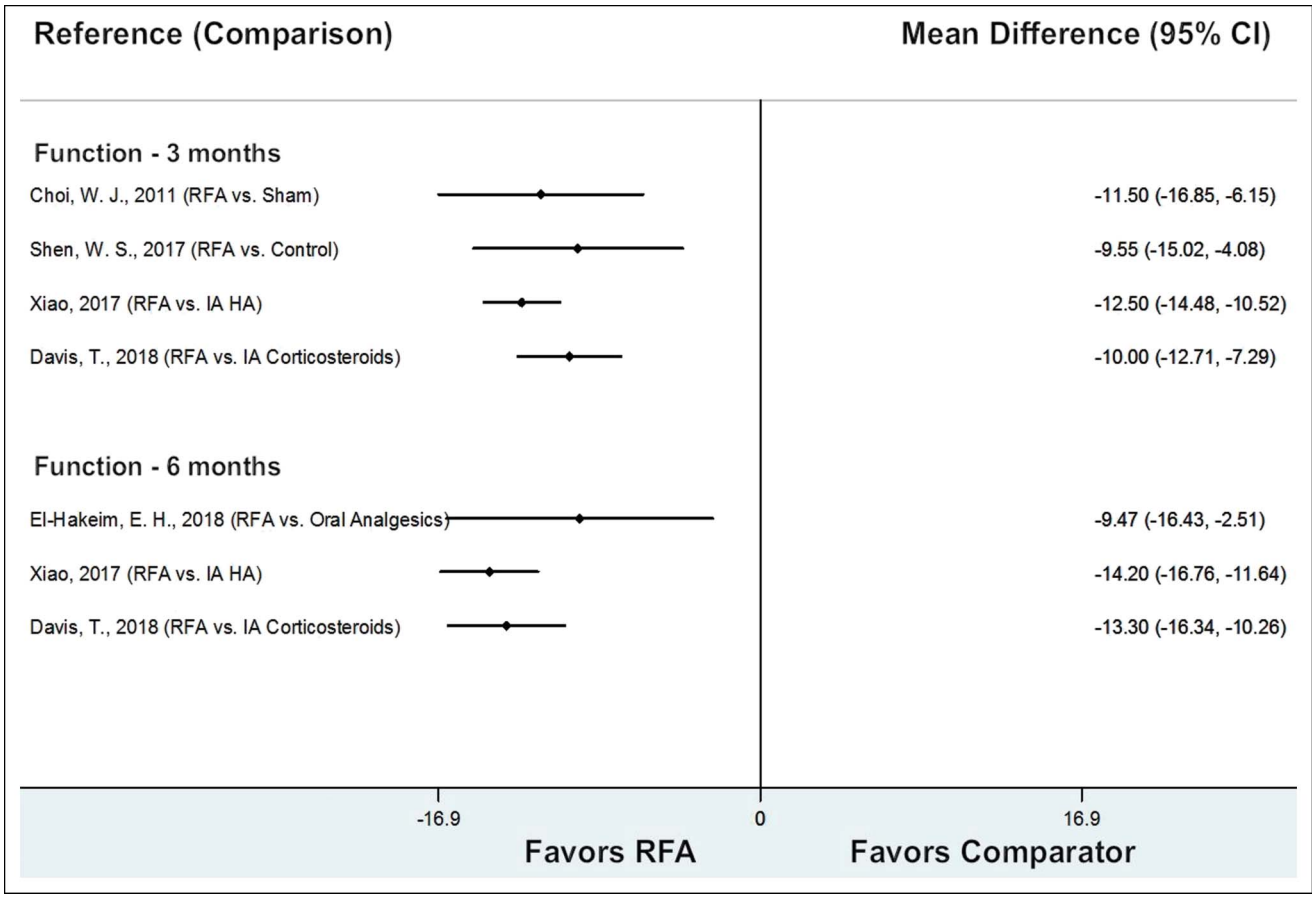

Chart showing functional outcomes of radiofrequency ablation (RFA) treatment comparisons. CI = confidence interval, HA = hyaluronic acid, IA = intra-articular

treatment comparisons. Four high-quality RCTs[27,29,31,32] showed that geniculate nerve RFA had favorable outcomes for overall WOMAC and GPE scores when compared with IA HA, IA corticosteroids, conventional oral nonopioid analgesics, and sham procedures (Figure 4). One high-quality RCT[29] found geniculate nerve RFA to be markedly favored over IA corticosteroids at 1 month for WOMAC total but did not find a notable difference at 3 months (Figure 4).

The magnitude and duration of knee OA pain relief for the three RCTs reporting outcomes at 6, 9, and 12 months are reported in Table 2. All three RCTs reported greater than a 4-point improvement in pain relief (>2 MCIDs) at all time points.[26-28] Clinically effective pain relief was noted at 6 months in two RCTs and at 12 months in one RCT.

Adverse Events

One high-quality RCT reported only minor AEs but found no statistical difference between study groups ($P = 0.56$), and no serious treatment-related AEs were reported.[26] One moderate-quality study did not report AEs.[30] All other studies reported zero treatment-related AEs.[27-29,31,32]

Full data reporting and quality appraisals can be found in the Supplemental Data File (Supplemental Digital Content 1, http://links.lww.com/JAAOS/A517).

Discussion

There are many different nonsurgical modalities for treating knee OA, but no systematic review has been performed evaluating the role of geniculate nerve RFA. This systematic review demonstrated that RFA of geniculate nerves was more effective at treating knee OA pain and function than current effective treatments, including NSAIDs (diclofenac) and IA corticosteroid injections. In addition, six of the seven RCTs found no serious AEs or complications related to thermal RFA as one RCT did not report AEs.

Figure 4

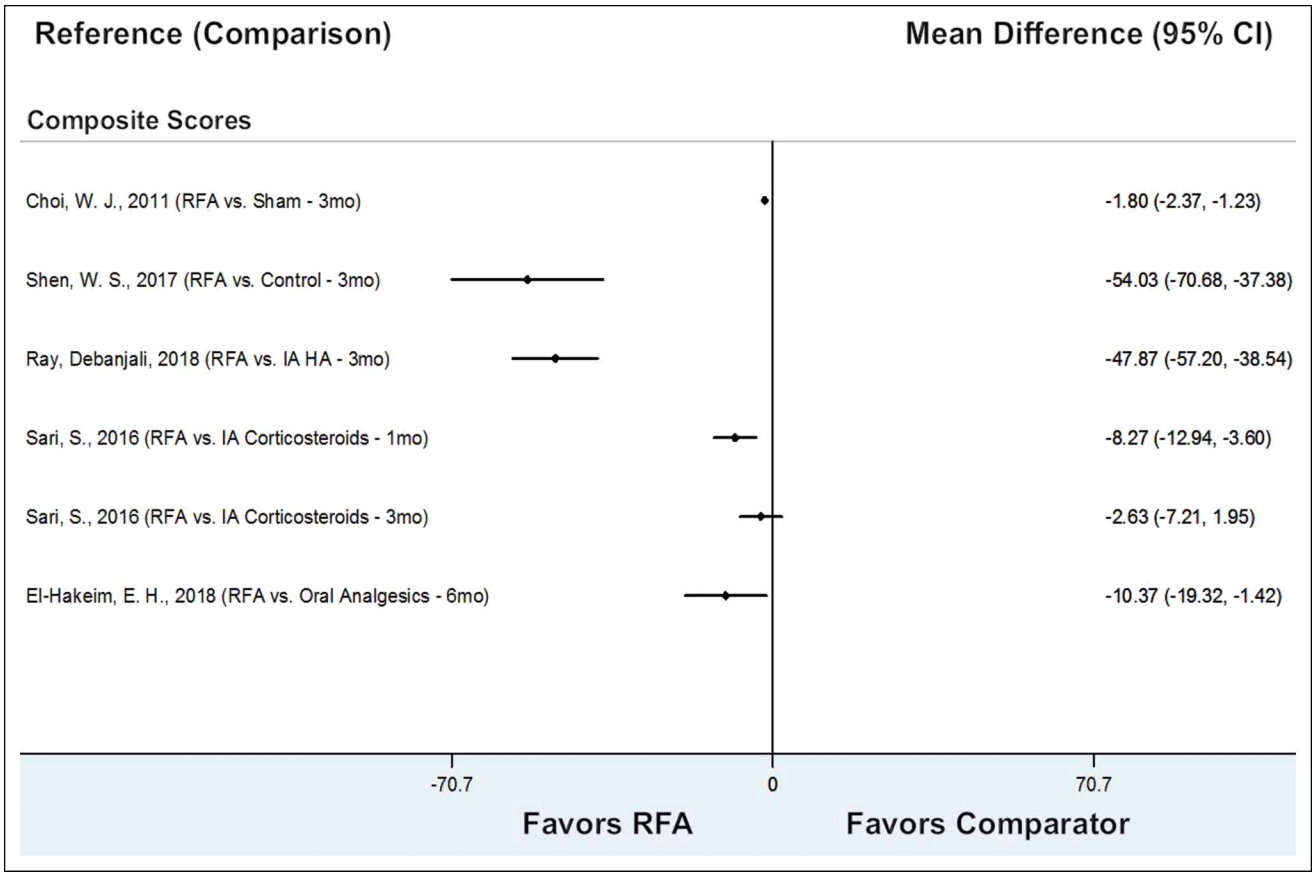

Chart showing composite patient outcomes of radiofrequency ablation (RFA) treatment comparisons. CI = confidence interval, HA = hyaluronic acid, IA = intra-articular

The duration of treatment effects is critical for cost effectiveness. The longer the treatment relieves knee pain, the more cost effective is the treatment. In a 2018 network meta-analysis of pharmacological treatments of patients with knee OA with "at least 12 months of follow-up, there was uncertainty around the estimates of

Table 2. Longer term Time Course of Knee Osteoarthritis Pain Relief Comparing Active Treatments

Study	Follow-up	RFA Mean Change in Pain Score (1)	RFA MCIDs (1)	Comparator Mean Change in Pain Score (2)	Comparator MCIDs (2)
Davis et al[26] RFA versus IA corticosteroid	3 mo	−4.4	−2.21	−1.9	−0.95
	6 mo	−4.9	−2.46	−1.3	−0.65
El-Hakeim et al[27] RFA versus diclofenac/ paracetamol	3 mo	−4.3	−2.16	−2.0	−1.01
	6 mo	−4.0	−2.01	−1.2	−0.60
Xiao et al[28] RFA versus IA hyaluronate	3 mo	−5.6	−2.81	−2.3	−1.16
	6 mo	−5.1	−2.56	−2.4	−1.21
	9 mo	−4.9	−2.46	−1.4	−0.70
	12 mo	−4.4	−2.21	−0.5	−0.25

IA = intra-articular, MCID = minimum clinically important difference, RFA = radiofrequency ablation

effect size for change in pain for all comparisons with placebo.[33]" Hunter et al[34] published follow-up of the Davis et al[26] RCT RFA cohort demonstrated that geniculate nerve RFA provided clinically notable relief at 12, 18, and 24 months. This is 16 times longer pain relief than IA corticosteroid injections, which are often only effective for 4 to 6 weeks.

Ajrawat et al[35] recently published a systematic review of radiofrequency procedures for the treatment of knee OA, which included 33 studies. The systematic review included 33 studies, but only 13 RCTs were included. The authors included RCTs assessing IA RFA[36] (not geniculate nerve RFA) and RCTs comparing RFA techniques with each other rather than comparison of RFA to other treatment options. Consequently, their findings are not specific to geniculate nerve thermal RFA. However, their findings of AEs are important. "Regarding AEs, 29 of 33 studies reported AEs, with 20/29 (69%) studies indicating no AEs related to the RF modalities and the remaining nine studies only indicating minor localized AEs. Twenty-nine of the 33 studies indicated no serious knee-related AEs pertaining to RF modalities.[35]"

These findings have several implications for the nonsurgical treatment of knee OA. Geniculate nerve RFA can be used in patients with contraindications to NSAID use, such as diabetes, renal disease, cardiovascular risk, and gastrointestinal risks. Thermal RFA is superior to IA corticosteroid injections with much longer duration of effectiveness (12 to 24 months versus 4 to 6 weeks) and does not have the risks of cartilage loss and periprosthetic infection associated with IA corticosteroids. Geniculate nerve thermal RFA can also be used in obese/morbidly obese patients or other patients requiring weight loss, smoking cessation, or other optimization before surgery.[37] However, the cost of this method of treatment is greater than other nonsurgical modalities for treating knee OA, including IA corticosteroids and NSAIDs, and may need to be performed in ambulatory surgery settings. On the other hand, it is the understanding of the authors that the costs of RFA are comparable with a series of three IA HA injections.[38] Geniculate nerve RFA are also commonly performed by individuals who receive specialized training, including pain management specialists, regional anesthesiologists or physical medicine, and rehabilitation physicians, which may be taught during residency/fellowship or can be acquired once in practice.

Ghomrawi et al[39] recently published an analysis on the "timeliness" of total knee arthroplasties in the United States. Their findings were that among the 8,002 patients; 294 knees or 26% of the 1,114 total knee arthroplasties performed were "likely inappropriate" and were performed prematurely. The authors cautioned that "[u]ndergoing TKA too early may result in little or no benefit while exposing the patient to risks of a major operation, ….[39]"The percentage of "premature" TKAs is remarkably similar to the percentages of patients not satisfied with their TKA (Robertsson et al 18%, Baker et al 18%, and Bourne et al 19%)[5-7] and the percentage of patients on opioids before TKA (Smith et al 23%, Bell et al 21%, and Bedard et al 29%).[40-42] A notable percentage of patients with knee OA are not able to manage their pain with nonsurgical treatments before they are appropriate candidates for TKA.

HA continues to be used despite the evidence that HA is not more effective than placebo.[43] One rationale for the use of HA is that other effective knee OA treatments have been tried or are contraindicated, so clinicians use HA injections and hope for a placebo effect with no AEs. Xiao et al[28] demonstrated that geniculate nerve thermal RFA is more effective than HA, not to mention that RFA is superior to NSAIDs and IA corticosteroids. Evidence supports the use of geniculate nerve thermal RFA instead of HA when other recommended treatments are ineffective or contraindicated.

In conclusion, thermal RFA of geniculate nerves is more effective at treating knee OA pain and function than current treatments including NSAIDs or IA corticosteroids, and the pain relief is clinically notable to 24 months.[34] No serious AEs were noted with the application of geniculate nerve thermal RFA in this systematic review or the systematic review by Ajrawat et al.[35] Future studies are needed to determine whether patients receiving geniculate nerve thermal RFA benefit from more than a single treatment to compare geniculate nerve thermal RFA to other NSAIDs and to determine whether geniculate nerve thermal RFA is associated with AEs or poorer outcomes if patients progress to TKA. The last prognostic question is best answered with registry data, so adding preoperative geniculate nerve thermal RFA treatment to the American Joint Replacement Registry data set would allow future analyses.

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