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INTERVENTIONAL RADIOLOGY

REVIEW

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Review of genicular artery embolization, radiofrequency ablation, and cryoneurolysis in the management of osteoarthritis-related knee pain

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ABSTRACT

Osteoarthritis (OA) of the knee represents one of the most common diseases in the world, affecting an estimated 14 million people in the United States alone. Exercise therapy and oral pain medication are first-line treatments but have limited efficacy. Next-line treatments such as intra-articular injections are limited in durability. Moreover, total knee replacements, although effective, require surgical intervention, which has considerable variability in patient satisfaction. Novel minimally invasive image-guided interventions are becoming more widespread for treating OA-related knee pain. Recent studies of these interventions have revealed promising results, minor complications, and reasonable patient satisfaction. In this study, published manuscripts were reviewed in the field of minimally invasive, image-guided interventions for OA-related knee pain, with a focus on genicular artery embolization, radiofrequency ablation, and cryoneurolysis. Recent studies have demonstrated a significant decrease in pain-related symptoms following these interventions. Reported complications were mild in the reviewed studies. Image-guided interventions for OA-related knee pain exist as valuable options for patients who fail other therapies, may not be good surgical candidates, or wish to avoid surgical intervention. Further studies with randomization and an increased length of follow-up are needed to better characterize outcomes following these minimally invasive therapies.

KEYWORDS

Cryoneurolysis, genicular artery embolization, knee pain, osteoarthritis, radiofrequency ablation

Osteoarthritis (OA) is a major public health problem, with a growing prevalence and incidence.[1] OA of the knee, in particular, affects an estimated 14 million people in the United States alone.[2,3] Furthermore, knee OA is not simply a disease of the elderly, as one in eight individuals with symptomatic knee OA are under the age of 45, and nearly half the patients with OA are between 45 and 64 years.[4] Symptoms of knee OA include stiffness, leading to a reduction in the range of motion, tenderness, and swelling; however, the most common presenting symptom of knee OA is knee pain.

The pathophysiology of OA is complex, and a clear mechanism has not been confirmed. However, a variety of factors, including cartilage breakdown, synovial inflammation, angiogenesis, and recruitment of inflammatory markers, are thought to be the primary drivers of disease progression.[5-8] Risk factors, such as age, obesity, smoking, and mechanical stress, contribute to the degradation of articulating hyaline cartilage, periarticular tissues, and subchondral bone in joints throughout the body.[9] This process leads to a state of chronic inflammation, which is characterized by the release of inflammatory cytokines, including tumor necrosis factor alpha, interleukin (IL)-1β, and IL-6.[10] These cytokines trigger pro-inflammatory processes over time, leading to the release of vascular growth factors, neuropeptides, and β nerve growth factor.[6-8] These markers stimulate the growth of new blood vessels through a process of neovascularization. New vasculature grows into the local joint space of the knee and penetrates adjacent cartilage, synovium, and bone.[5] New blood vessels may also contribute to the growth and development of new sensory nerve fibers.[5] The common pain experienced by people with knee OA is likely a result of a combination of factors, including chronic inflammation, mechanical stress, and the development of unmyelinated nerve fibers along sites of neovascularity and chronic inflammation.

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Current treatment options for symptomatic knee OA aim to limit pain symptoms. Exercise therapy is a first-line treatment for symptomatic OA because of its lack of adverse side effects, cost effectiveness, and reasonable efficacy.[11,12] The limitations of this therapy include poor adherence, observed in a majority of patients, as well as the inability to perform the exercises when pain levels become high.[13] Patients often progress to using over-the-counter pain medication, such as non-steroidal anti-inflammatories (NSAIDs), for the relief of symptoms. However, NSAIDs subject patients to the risks of gastrointestinal bleeding, kidney injury, and gastric ulcers.[14] Intra-articular steroid and hyaluronic acid injections may provide relief, but the benefits are not durable and have been shown in some studies to accelerate knee OA progression.[15-17] Total knee replacement (TKR) is reserved for patients with severe OA that is refractory to conservative therapy, and patients often suffer with OA-related knee pain symptoms for an average of 9 years prior to becoming surgical candidates.[18] More than 20% of patients receiving TKR experience persistent and unchanged pain after their surgery.[19-21]

In this context, novel minimally invasive interventions for OA-related knee pain may improve patient outcomes and satisfaction. Image-guided interventions for OA-related knee pain consist of varied minimally invasive procedures that include genicular artery embolization (GAE), radiofrequency ablation (RFA), and cryoablation. These interventions are becoming increasingly common given their safety profile and ability to be performed on an outpatient basis.[22] Recent studies of the modalities, which are discussed in this paper, have demonstrated promising results in the management of OA-related knee pain.

Main points

- Osteoarthritis (OA) is one of the most prevalent diseases in the world, with pain as the most common presenting symptom, necessitating the need for effective and safe treatment.
- Although current options for osteoarthritic knee pain relief exist, they are not without side effects and have varying levels of efficacy.
- Minimally invasive options such as genicular artery embolization, radiofrequency ablation, and cryoneurolysis have been demonstrated to produce significant pain relief in randomized controlled trials, and although further research is required to fully characterize their place in OA-related pain treatment, the use of these treatments should be considered.

Discussion

Genicular artery embolization

As previously discussed, neovascularity and its association with synovial inflammation may contribute to the progression of OA-related knee pain. Although other treatment options aim to specifically treat symptoms of pain through the disruption of pain signaling pathways, GAE aims to occlude synovial neovascularity in an effort to decrease the contribution of synovial inflammation to disease progression.[22]

The knee joint is classically supplied by six genicular arteries: a descending genicular artery, superior medial genicular artery, inferior medial genicular artery, superior lateral genicular artery, inferior lateral genicular artery, and anterior tibial recurrent artery (Figure 1). The descending genicular artery branches off from the distal superficial femoral artery. The medial and lateral genicular arteries originate from the popliteal artery, and as the names imply, superior genicular arteries course along the superior aspect of the knee, and inferior genicular arteries course along the inferior portion of the knee. GAE is performed by obtaining arterial access, commonly through the femoral artery, and guiding a microcatheter to the specific genicular arteries in the areas of reported pain. When the proper location is confirmed through fluoroscopy, an injection of embolization particles is administered if neovascularity and hyperemia are demonstrated.

Inflamed synovium neovascularity can be seen on angiography as a contrast-rich area reflecting synovial hyperemia (Figure 2a). The goal of GAE is to prune the neovascularity supplying the hyperemic region, thereby reducing the hyperemia and inflammation of the synovium (Figure 2b).[23] Embolization can be accomplished through the injection of permanent particles or temporary embolic agents into targeted vasculature.[23-26] Figure 3 presents a diagram of GAE.

Several studies have been conducted on the efficacy of GAE in treating OA-related knee pain. Okuno et al.[26] conducted a study in 2017 of 72 patients, defining the clinical success of GAE as a 50% reduction in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score versus baseline. The WOMAC score is used in the setting of hip and knee OA and ranges from 0 to 96.[27] It consists of a self-administered questionnaire, which has 24 items and is divided into three categories: pain, stiffness, and physical function. The results of the study reveal a clinical success rate of 86.3% and 79.8% at 6 months and 3 years, respectively.

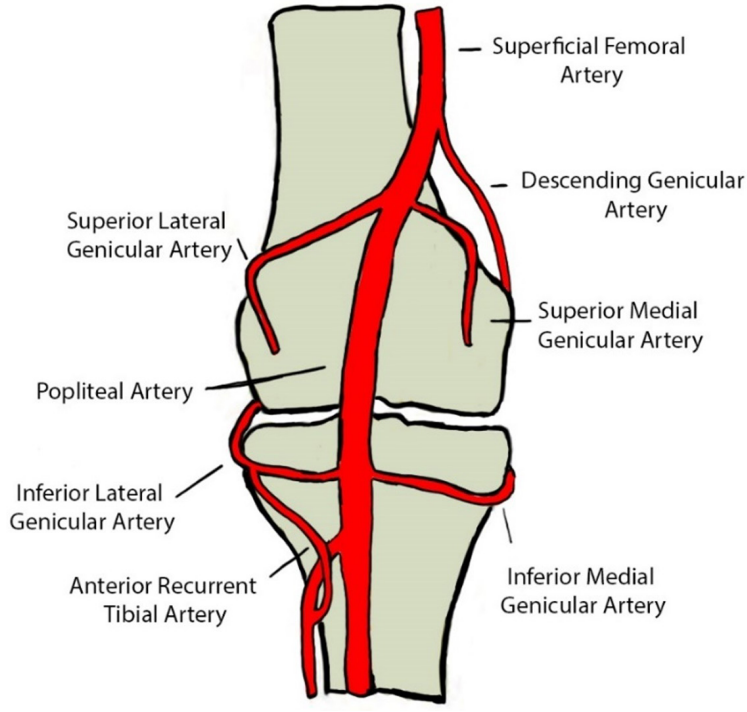

Figure 1. Vascular supply to the knee.

A study in 2020 by Landers et al.[25] included 10 patients at 1-, 6-, and 12-month postprocedure follow-up. Of these 10 patients, two withdrew from the study, with one undergoing a TKR with no reported benefit. This study reported an inferior treatment response compared with the findings of Okuno et al.[28], with a 60% response rate to intervention at 12 months. At 24 months, although the quality-of-life scores and 30-s chair stand test performance were substantially improved from baseline, pain and self-reported function returned to near baseline levels.

The GENESIS Trial, published in 2021, was a prospective trial including 38 patients [Kellgren–Lawrence (KL) grade 1–3] and a mean follow-up of 8 months.[23] Synovial hypervascularity was assessed through magnetic resonance imaging (MRI) to standardize the preprocedure and postprocedure imaging assessment. Significant reductions in pain were noted, measured using the knee injury and OA outcome score, at 6 weeks and 12 months. An MRI analysis revealed improvement in synovitis across all patients and an absence of postembolization cartilage loss.[28,29]

In 2022, Bagla et al.[30] conducted a randomized controlled trial consisting of GAE compared with a sham procedure in 21 patients over the course of 12 months. Patients randomized to the sham cohort had no significant reduction in pain at 1 month and were moved to the GAE cohort. At 12 months, patients receiving GAE exhibited a statistically significant mean reduction in both WOMAC pain scores (47) and Visual Analog Scale scores (54.6). Three patients withdrew from the trial because of increased pain from baseline following the GAE procedure. Similarly, the patients who moved to the treatment cohort exhibited statistically significant reductions in pain scores at all time points.

The potential complications of GAE include nerve injury, bone infarction, access site hematoma, skin erythema and ulceration, and non-target embolization.[28,31-33] To better predict a patient's response to GAE, studies have researched patient factors associated with inferior treatment outcomes.[31,33] Having a better understanding of these factors can potentially aid patient selection and improve the risk–benefit profile of the intervention. A study published in 2021 specifically focused on MRI findings in patients who underwent GAE.[33] The strongest predictor of diminished pain reduction after GAE, measured using the WOMAC score, was the presence of a full-thickness cartilage defect. Effusion synovitis, high-grade osteophytes, bone marrow lesions, and subregional cartilage lesions (all associated with a higher KL grade) were variables associated with decreased pain reduction. These findings suggest that MRI may be used to identify patients less likely to respond to GAE therapy.

Recent studies regarding GAE as a therapeutic option have demonstrated promising results. To further our understanding of GAE, additional randomized sham-controlled trials should be undertaken.

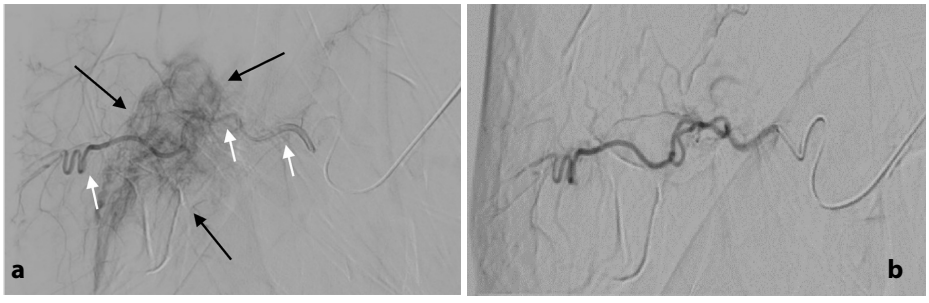

Figure 2. (a) Angiogram of the superior lateral genicular artery (white arrows) indicating hyperemia (black arrows) in the perfused territory. **(b)** Angiogram following genicular artery embolization showing the resolution of hyperemia in the perfused territory.

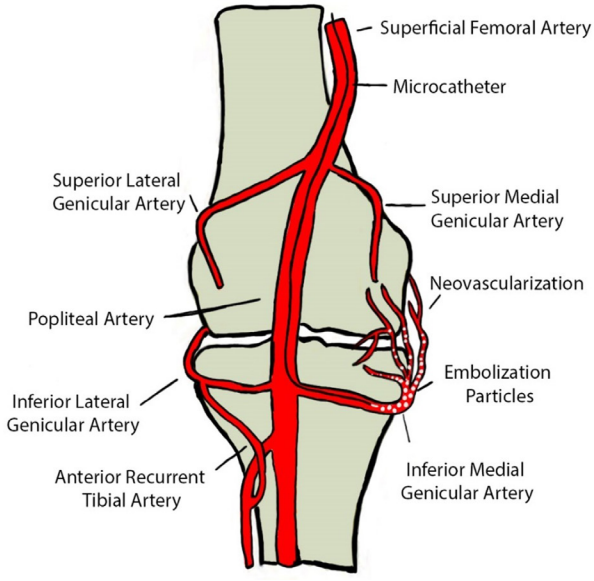

Figure 3. Genicular artery embolization procedure with embolization particles injected into the inferior medial genicular artery.

RFA

RFA was first described in 1891. It functions by creating an electromagnetic field around the tip of a device that transfers heat energy to adjacent structures.[34] This procedure has been used to treat conditions such as trigeminal neuralgia, lumbar spinal facet disease, and sacroiliac joint pain, as well as OA-related knee pain.[35-37] RFA ablation may be particularly useful for treating OA-related knee pain because of its targeted effect on neuropathic pain. The successful ablation of nerves prevents the transmission of pain signals sent as a result of chronic inflammation and direct bony contact in the context of OA.[38,39] Different options exist concerning the temperature range of the probe as well as the option of pulsed application.[40] Traditionally, the goal temperature ranges from 70 °C–90 °C, but recent studies have employed temperatures as low as 60 °C.[41]

Given that the genicular nerves supplying the knee consist of branches of the femoral, common peroneal, saphenous, tibial, and obturator nerves, multiple targets exist for ablation in an attempt to treat intra-articular nerve endings and inhibit the neurotransmission of nociceptive signals.[32,40,42] Commonly targeted nerves for OA-related knee pain include the superior lateral, superior medial, and inferior medial genicular nerves. Due to the role of the common peroneal nerve in motor control and the potential risk of motor nerve injury, the nearby inferior lateral genicular nerve is rarely targeted.[43] The

accurate placement of the RFA probe is made possible by using fluoroscopic guidance and ultrasound imaging.[22] Potential candidates undergo a diagnostic extra-articular injection with local anesthetic as a trial to assess whether the pain relief in the target area is adequate over a course of at least 24 hours. If significant pain relief is achieved, RFA may be scheduled. In this procedure, electrodes are placed using cannulas that are percutaneously stationed at the target area. Sensory and motor stimulation is performed prior to the ablation to ensure proper placement.[44] A diagram of the RFA procedure is shown in Figure 4.

Recent studies have focused on specific temperatures for RFA. A prospective randomized controlled study examined the use of cooled RFA (60 °C).[41] Cooler temperatures may change the shape of the ablation zone from ellipsoid to spherical, thereby affecting a greater area with less risk of thermal injury and complications.[41,45-48] Chen et al.[41] found that cooled RFA, when compared with hyaluronic acid injections, is effective at pain relief, reduction of stiffness, and improvement in physical function as well as global outcomes and quality of life at 12 months, shown as a 46.2% improvement in the WOMAC score.

Pulsed frequencies are often used instead of continuous radiofrequency in RFA. The use of a pulsed frequency has less potential for nerve injury.[49,50] Previous studies of RFA have indicated lower pain scores during follow-up when compared with placebo, with some studies demonstrating up to a >50% decrease in pain scores over a 6-month period.[35,49] A study by Masala et al.[42] in 2014 revealed a significant decrease in pain scores at 12-month follow-up and improved autonomy in daily life demonstrated by an improvement in the WOMAC score from a baseline of 67 to 21, 20, 23, and 30 at 1, 3, 6, and 12 months, respectively. A further study that combined pulsed RFA with viscosupplementations noted that knee pain, although lower than baseline, returned at the 12-month follow-up, suggesting a need for potential future reintervention in the case of pain recurrence.[51]

A recent meta-analysis of RFA completed by Zhang et al.[52] analyzed nine randomized controlled trials and included 802 patients. Their analysis revealed improvements in pain scores at 4, 12, and 24 weeks compared with placebo, with a statistically significant weighted mean difference between WOMAC scores at 12 and 24 weeks of 4.53 and 2.99, respectively. Another systematic review of 33 articles, including 13 randomized controlled trials, revealed a similar alleviation of OA pain symptoms, improvements in quality of life, and enhanced functionality for up to 3–12 months following intervention.[53] Six of these studies had clearly defined significant pain improvements with a >50% reduction from baseline, which was achieved by 65.5% of patients in the RFA group and only 19.3% in the control group. This analysis included studies using continuous RFA, pulsed RFA, and cooled RFA, with benefits seen in all three modalities.

The risks of RFA are mostly associated with injury to adjacent structures. Complications include pseudoaneurysm, arteriovenous fistula development, hemarthrosis, and osteonecrosis.[52,53] One study from the previously mentioned meta-analyses reported the development of pes anserine injury of the inferior medial genicular nerve following RFA.[54] Contraindications of RFA include uncontrolled diabetes, bleeding disorders, the presence of an implantable defibrillator or pacemaker, and knee infection.[17] The large number of studies demonstrating the success of RFA suggests that it is a valuable minimally invasive treatment option for symptomatic OA of the knee. Patients are generally satisfied with the procedure and note improvements in pain, functionality, and quality of life. Studies with larger populations and longer-term follow-up would be useful to evaluate the durability of the symptomatic benefits of RFA as well as the potential impact on the knee joint.

Cryoneurolysis

Similar to RFA, cryoneurolysis, or cryotherapy, aims to damage the nerve endings responsible for the pain experienced in knee OA.[22] As the name implies, this process is completed by using a cooling probe with temperatures ranging from −20 °C to −100 °C. The first reported use of cryoanalgesia was in 1963, when Irving S. Cooper used a hollow tube filled with liquid nitrogen.[55] Marked technological advancements have occurred since then to further develop the equipment and applications of this interventional treatment.[56] Cryoneurolysis leads to the Wallerian degeneration of nerves, which occurs when the distal portion of an injured nerve begins to progressively degenerate as both axon and myelin are broken down by macrophages.[57,58] This controlled, mild nerve damage allows for the complete regeneration and recovery of nerve function by preserving the structural elements of the nerve.[59-61] The cryoablation of these nerves leads to the decreased transmission of pain signals and disruption of the regulation of the IL-6 and IL-17 cytokine pathway observed in the chronic inflammatory state.[10] The infrapatellar branch of the saphenous nerve, which innervates the anterior and inferior part of the knee capsule and skin over the anteromedial knee, is often targeted for this procedure.[62] The specific location for innerva-

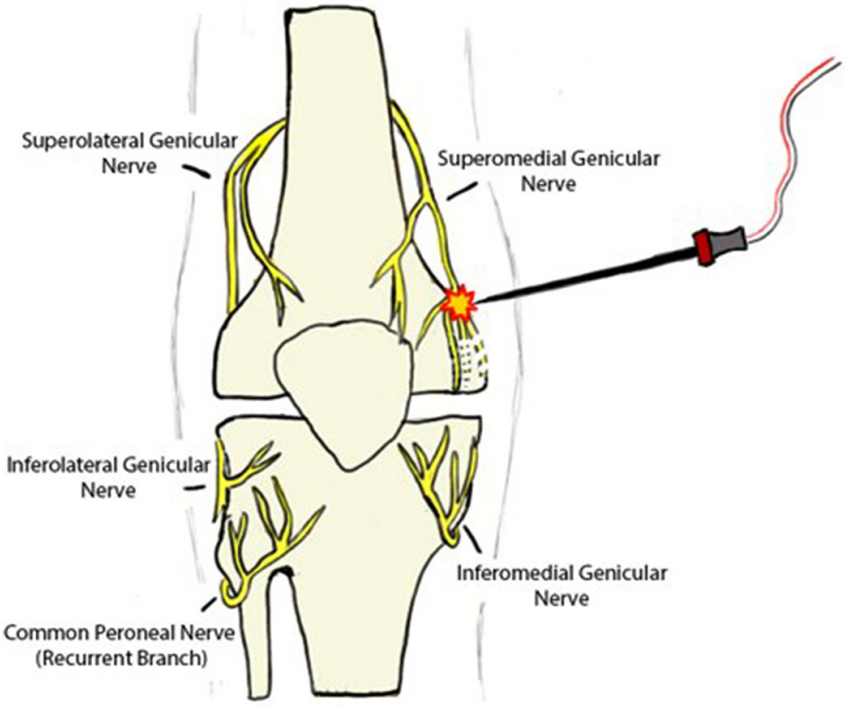

Figure 4. Radiofrequency ablation procedure with ablation to the superomedial genicular nerve.

tion is determined by transcutaneous nerve stimulation in the area of reported pain. The cooling probe can then be placed using ultrasound guidance prior to the cooling process.

Data on cryoneurolysis for OA-related knee pain is limited. A randomized controlled trial conducted by Radnovich et al.[57] included a total of 180 patients and compared cryoneurolysis to a sham procedure in the treatment of knee OA. During this trial period, patients discontinued all over-the-counter medications, herbal medications, and other treatments. An improvement in WOMAC score of 7.1 points at 1 month and 4.7 points at 2 months was identified when compared to the sham procedure.

The effectiveness of the procedure seems to depend on the proximity of the probe to the nerve, size of the probe, rate and duration of treatment, and temperature.[57,62,63] A major benefit of cryoneurolysis is its safety profile and the temporary effect on the treated nerve.[64,65] The risks of this intervention include damage to the skin, alopecia, depigmentation of the skin, and damage to surrounding structures.[66] Although cryoneurolysis has been used in many other applications, more studies are needed to assess efficacy, durability, and complications from this treatment in patients with knee OA.

In conclusion, the widespread prevalence of knee OA as a cause of daily pain and disability warrants an in-depth investigation into novel minimally invasive image-guided therapies. Although exercise, physical therapy, oral medications, joint injections, and joint replacement are mainstays of treatment, image-guided interventions have also entered the treatment landscape. This manuscript discusses minimally invasive image-guided interventions in the treatment of OA-related knee pain. Genicular artery embolization, RFA, and cryoablation have strong safety profiles, can be performed on an outpatient basis, and have been shown to significantly decrease pain scores. GAE recently exhibited promising results in decreasing pain scores and improving quality of life, but current studies have relatively small patient samples without randomization. RFA has been performed for decades, and recent modifications in temperature and pulsatility of frequency are being used to provide positive results. Cryoneurolysis for OA-related knee pain has limited data but has been shown to provide temporary pain relief with limited and minor complications. Although these results are certainly promising, further studies, specifically additional randomized controlled trials with placebo cohorts and extended durations of follow-up, are needed to advance our understanding of these minimally invasive treatments and establish where they fit in the algorithm of OA therapies.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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