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REVIEW ARTICLE

Genicular artery embolization as a treatment for refractory osteoarthritis related knee pain

Yan Epelboym[1] · Lynden Lee[2] · Yuji Okuno[3] · Amine Korchi[4]

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Abstract
Genicular artery embolization (GAE) is a minimally invasive outpatient therapy for osteoarthritis (OA) related knee pain, refractory to conservative management. This intervention targets neovasculature which arises in the setting of angiogenesis in OA. Various clinical trials highlighted in this manuscript suggest that GAE is effective in durably reducing OA-related knee pain, with a limited adverse event profile. This review also explores the clinical evaluation of GAE candidates, genicular artery anatomy, technical components of the procedure, and imaging from various GAE embolizations. It also discusses future directions for research which may illuminate predictors of clinical success as well as avenues for evolution in the GAE treatment.

Keywords Embolization · Osteoarthritis · Genicular

Introduction

Knee osteoarthritis (OA) is a chronic painful condition that affects the quality of life of millions of people around the world. Its pathophysiology is complex and involves joint inflammation, neovascularization, and sensory nerve growth [1–5]. Multiple therapeutic options are available for OA-related knee pain, ranging from noninvasive physical therapy to invasive knee replacement surgery. But despite this armamentarium of therapies, a significant proportion of patients still suffer from refractory knee pain [6, 7]. Genicular artery embolization (GAE) is a minimally invasive procedure that occludes neovascularity in the knee joint, thereby reducing inflammation and pain [8–10]. The procedure has been evaluated in multiple trials and shown to be safe, durable, and effective [8–15]. Historically, the GAE procedure was used as a treatment for recurrent hemarthrosis following knee replacement. However, in the past decade, research has evaluated the role of GAE in treating knee pain [16]. We aim to review relevant components of GAE in OA including pathophysiology, vascular anatomy, imaging, technical components of the procedure, and future directions for research.

The Unmet Need in Osteoarthritis Therapy

Symptomatic knee osteoarthritis (OA) affects more than 9.3 million American adults. Approximately 10% of individuals over the age of 55 are affected by disabling knee OA symptoms [17–19]. Once diagnosed, individuals on average live for 26 years with painful symptoms [20]. Multiple treatments are available for OA-related knee pain, including pharmacologic therapies, physical therapy, intraarticular injections, and, for severe OA, total knee arthroplasty. While oral medications such as acetaminophen, non-steroidal anti-inflammatories, opiates, and intra-articular injections seek

✉ Yan Epelboym
yepelboym@bwh.harvard.edu

Lynden Lee
llee4@mail.einstein.edu

Yuji Okuno
okuno@okuno-y-clinic.com

Amine Korchi
amine.korchi@gmail.com

[1] Department of Radiology, Division of Angiography and Interventional Radiology, Brigham & Women's Hospital, Harvard Medical School, Boston, USA

[2] Department of Radiology, University of California, Los Angeles, Los Angeles, USA

[3] Musculoskeletal Intervention Center, Okuno Clinic, 4th Fl Ginrei Bldg, 7-8-4 Minato-ku, Roppongi, Tokyo 106-0032, Japan

[4] Imaging Center Onex, Geneva, Switzerland

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to manage symptoms, adequate symptom control can be difficult to achieve [6, 7]. Mainstays of pharmacologic therapy for knee pain have limited efficacy and subject the patient to potential risks of liver dysfunction, renal dysfunction, gastrointestinal ulceration, and opiate addiction [6, 7]. Meanwhile, steroid and hyaluronic acid intra-articular injections demonstrate limited short-term efficacy and require repetitive treatment [6, 7]. Furthermore, awareness of potential risks of intra-articular steroid injections such as accelerated OA progression, subchondral insufficiency fractures, osteonecrosis, and joint destruction has been structurally reported and require further investigation [21].

Patients who develop severe OA become surgical candidates for knee arthroplasty; however, some patients may be poor surgical candidates or may wish to avoid surgery. Others may live for many years awaiting surgical candidacy. In this context, patients with painful knee OA who are not candidates for TKA or who prefer minimally invasive interventions can be considered for GAE.

Pathophysiology and Rationale

Osteoarthritis is a complex disease that develops in the context of aging, joint stresses, inflammation, and angiogenesis. Its pathophysiology is not completely understood and extends beyond the traditional biomechanical model of cartilage wear and tear. Osteoarthritis reflects a complex interplay between biomechanical and biochemical processes [1]. Preclinical and clinical studies have shown that peri-articular soft tissues, synovium, and inflammation are related to disease development [2, 3]. Inflammation and angiogenesis are intertwined with one process contributing to the progression of the other. In addition, angiogenesis is associated with sprouting of sensory nerves which contribute to joint pain [4, 5]. Given the relationship of inflammation, angiogenesis, and pain-inducing sensory nerve fibers, the opportunity arises for targeted treatment of the sites of angiogenesis. In embolizing the abnormal hyperemic knee vasculature, the potential arises for inhibiting angiogenesis, inflammation, neural sprouting, and pain.

Assessing GAE Candidacy

Patients with refractory OA pain symptoms who are not surgical candidates or prefer to avoid surgery can be considered for GAE. In addition to history, physical examination, and imaging demonstrating OA, specific clinical assessments prior to GAE intervention are recommended. Given the endovascular nature of the intervention, patients should be screened for symptoms of peripheral arterial disease (PAD) by history and lower extremity pulse exam. If there is concern for peripheral artery disease (PAD), pre-procedure Doppler ultrasound or CT angiography can be performed. Patients with PAD may be at higher risk of atheroembolic or arterial dissection complications for this endovascular procedure. In addition, patients with severe PAD may rely on genicular artery collaterals for perfusion of the lower extremity, and embolization of these genicular vessels would be contraindicated. In these patients, genicular nerve ablation may be considered as the procedure is performed percutaneously and does not require an endovascular approach [22]. Given utilization of iodinated contrast agents, baseline renal function should be assessed to minimize risk of renal injury. Baseline dermatologic evaluation of the knee should also be performed given the potential risks of GAE as it pertains to transient skin mottling.

Genicular Artery Anatomy

Performing genicular artery embolization requires detailed anatomic knowledge so that the procedure can be performed safely and effectively. The knee is typically supplied by 8 arteries: the descending genicular artery (DGA), superior lateral genicular artery (SLGA), superior medial genicular artery (SMGA), middle genicular artery (MGA), inferior lateral genicular artery (ILGA), inferior medial genicular artery (IMGA), anterior tibial recurrent artery (ATRA), and superior patellar artery (SPA). Conventional genicular artery anatomy can be seen in the figures below (Figs. 1, 2, 3, 4, 5, 6, 7, and 8).

Substantial variation in genicular artery anatomy exists and is important for the interventional radiologist to appreciate. Two recent studies utilizing cadaveric anatomy have offered a comprehensive classification system for both variations in branching as well as the presence of arterial anastomoses [23, 24]. Understanding this anatomy is critical for performing the intervention safely and effectively.

Arterial anastomoses are important to consider during embolization procedures given the possibility of non-target embolization via anastomoses. When viewing the medial compartment of the knee, anastomoses were present between the DGA and SMGA in 85% of cases. A branch connecting the SMGA and the popliteal artery was observed in 15% of cases and DGA to popliteal artery in 10% of cases. All anastomoses had a diameter greater than 300 microns, which was considered significant for risk of retrograde flow of embolic particles to unwanted territories. The relatively high proportion of variant anatomy and presence of anastomoses found between the previous two studies necessitates recognition of collaterals and changes in flow dynamics via anastomoses, when performing embolization.

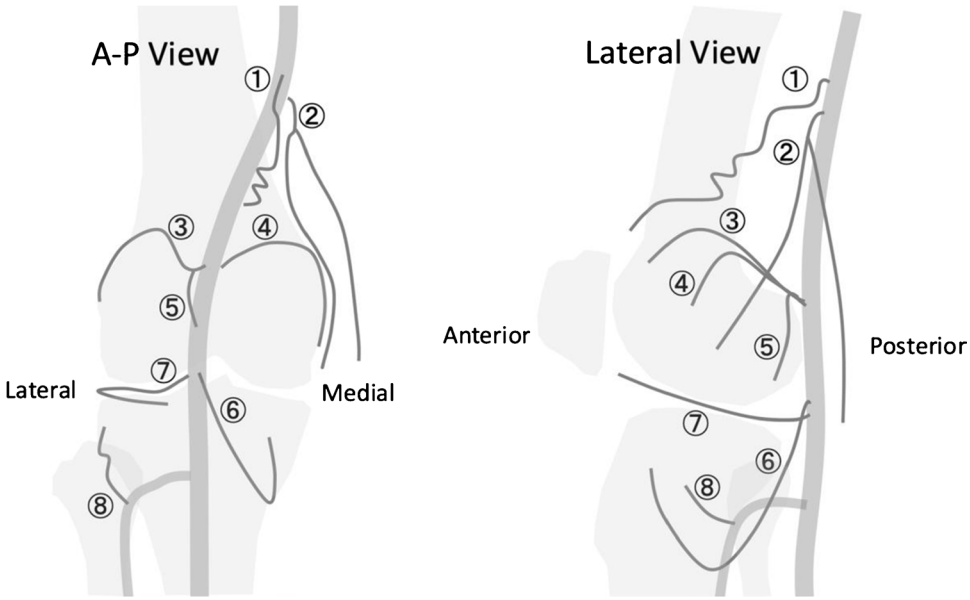

Fig. 1 (1) Superior patellar artery (SPA). (2) Descending genicular artery (DGA). (3) Superior lateral genicular artery (SLGA). (4) Superior medial genicular artery (SMGA). (5) Middle genicular artery (MGA). (6) Inferior medial genicular artery (IMGA). (7) Inferior lateral genicular artery (ILGA). (8) Anterior tibial recurrent artery (ATRA)

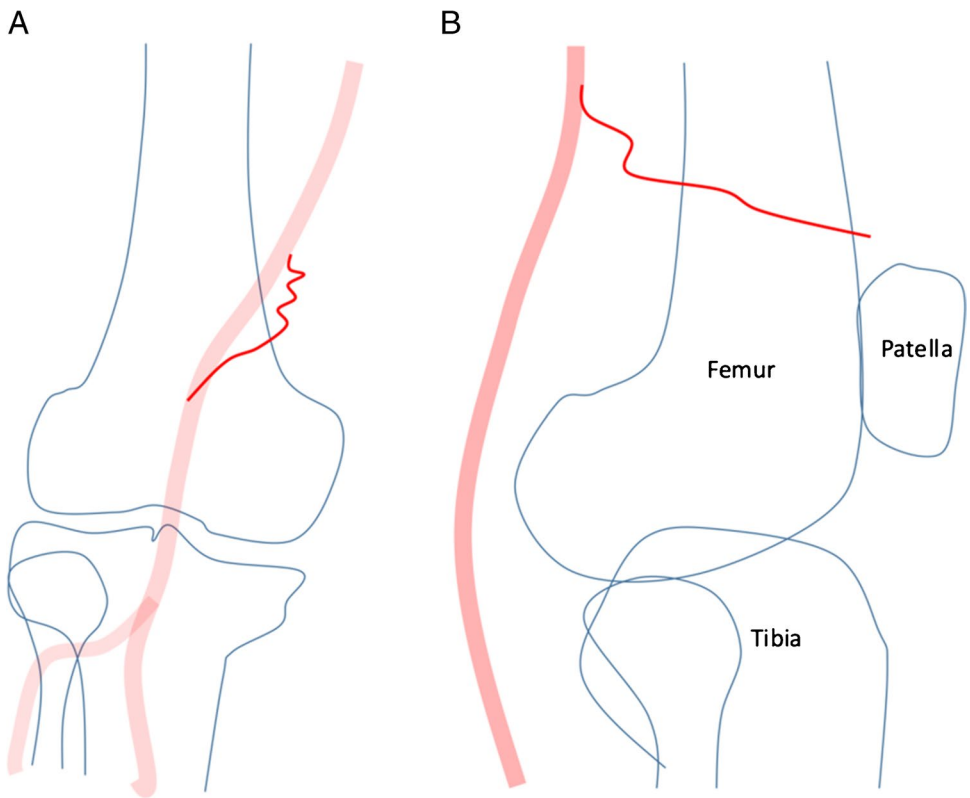

Fig. 2 **A** A-P view of superior patellar artery. **B** Lateral view of in superior patellar artery

GAE Embolization

Angiography

To guide vessel targeting, a skin radiopaque marker can be placed in the patients' self-reported area of maximal knee pain. Using local anesthesia and conscious sedation, antegrade ipsilateral or retrograde contralateral femoral arterial access can be obtained under ultrasound guidance using a 21-gauge needle. If contralateral access is obtained, a sheath ranging from 4 to 6 French in caliber is placed. A catheter is advanced into the contralateral

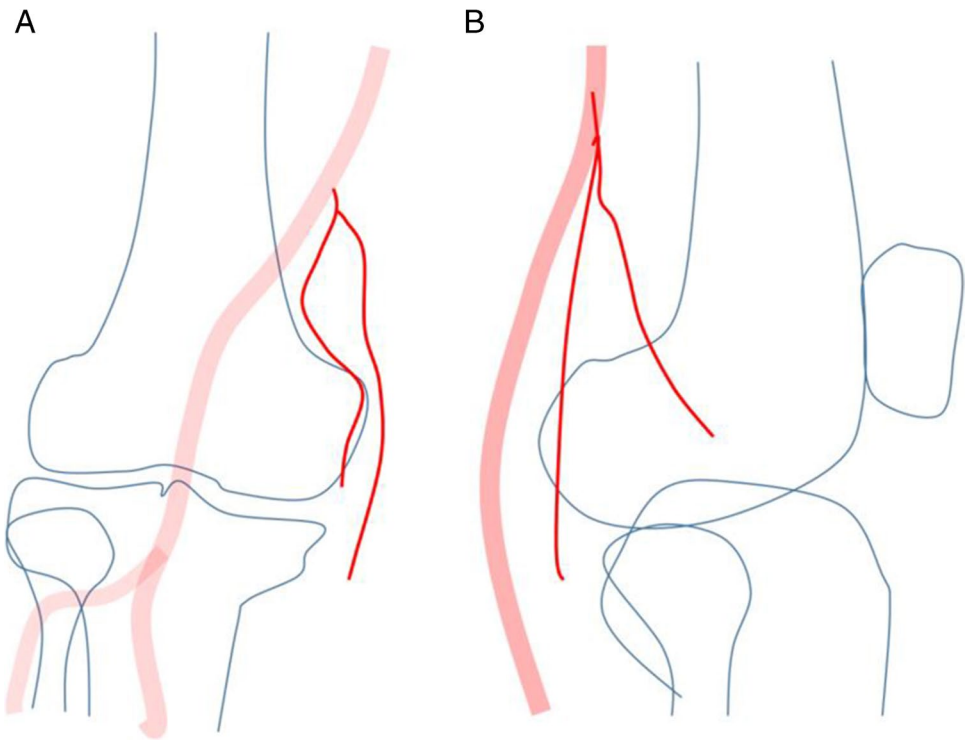

Fig. 3 **A** A-P view descending genicular artery. **B** Lateral View descending genicular artery

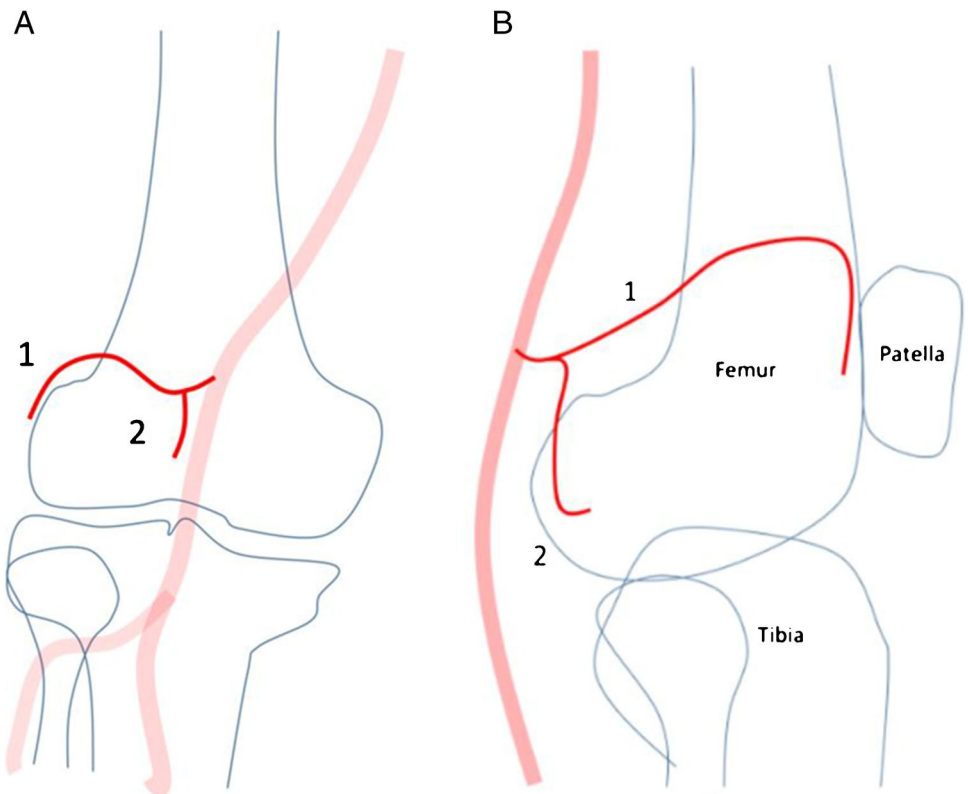

Fig. 4 **A** A-P view of superior lateral genicular artery (1) and middle genicular artery (2). **B** Lateral view of superior lateral genicular artery (1) and middle genicular artery (2)

limb, and digital subtraction angiography is performed to delineate the arterial branches of the superficial femoral artery and popliteal artery. Alternatively, if ipsilateral access is obtained, a 3 French sheath may be placed and angiography of the superficial femoral and popliteal arteries may be performed via the sheath. Regions of the knee

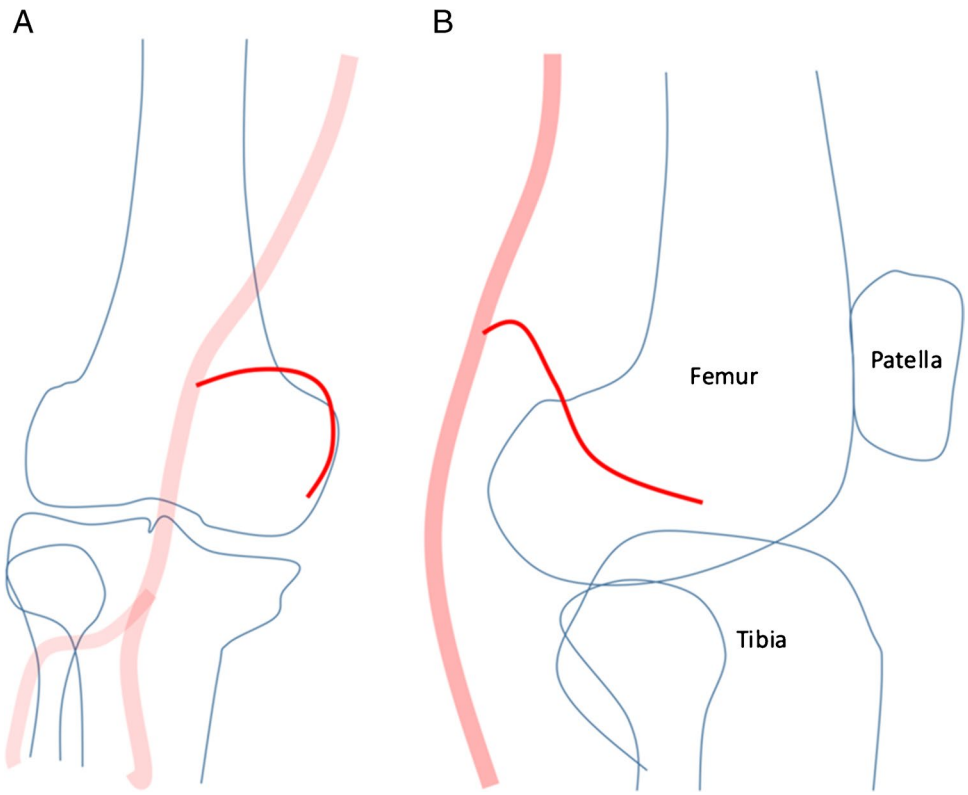

Fig. 5 **A** A-P view of superior medial genicular artery. **B** Lateral view of superior medial genicular artery

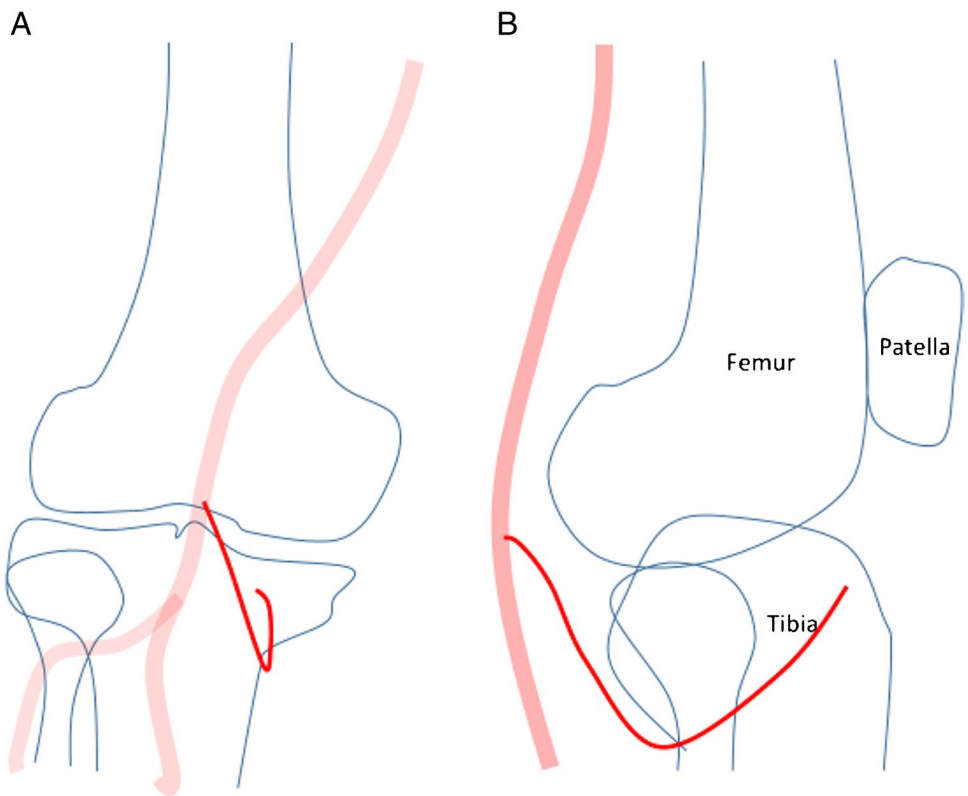

Fig. 6 **A** A-P view of inferior medial genicular artery. **B** Lateral view of inferior medial genicular artery

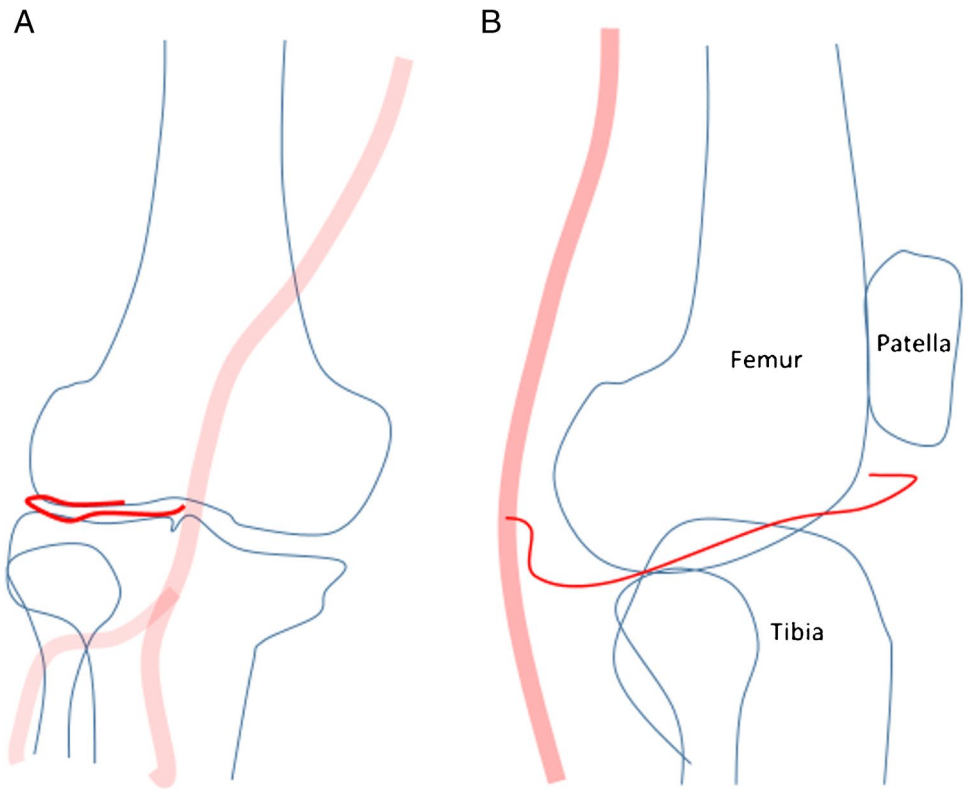

Fig. 7 **A** A-P view of inferior lateral genicular artery. **B** Lateral view of inferior lateral genicular artery

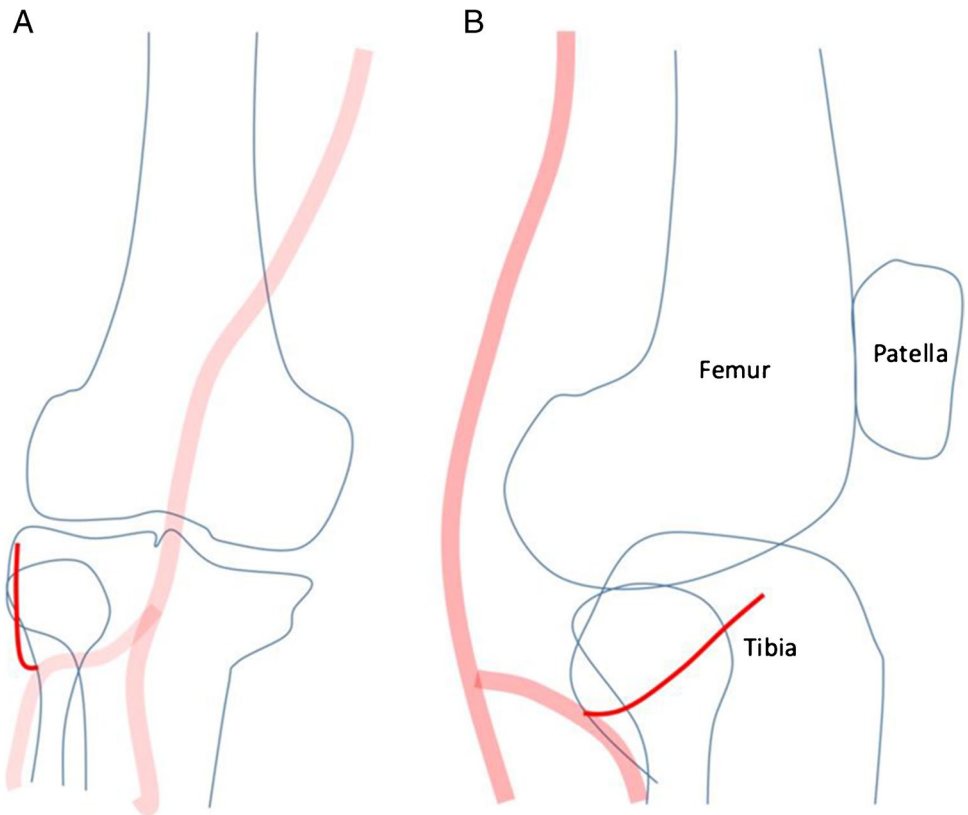

Fig. 8 **A** A-P view of anterior tibial recurrent artery. **B** Lateral view of in anterior tibial recurrent artery

with hyperemia are identified. Distinct genicular arteries corresponding to the regions of pain or hyperemia are then selected with a microcatheter and microwire. With the microcatheter in the selected genicular artery, digital subtraction angiography is performed to identify neovascularity and hyperemia.

Embolization

Immediately prior to performing embolization, an ice pack is placed on the skin surface of the knee to be embolized. The purpose of the ice pack is to vasoconstrict the superficial arteries of the skin, in order to minimize risk of skin injury. Particle embolics have typically been used in GAE and are available in two broad categories, temporary vs. permanent. Temporary embolics such as imipenem-cilastatin sodium (IPM-CS) in suspension or calibrated gelatin sponge particles have been used [8–10]. Imipenem-cilastatin sodium, which has been employed outside of the USA, forms 10–70-um crystals when suspended in contrast. In the USA and UK, permanent embolic microparticles have been used in calibers ranging from 75 to 300 um [11–13, 15].

Embolization is performed by gently injecting small aliquots of embolic (0.1 to 0.3 mL) and then performing angiography. This process is serially repeated until hyperemia is no longer demonstrated and pruning of the distal hypervascular branches has taken place (Figs. 9, 10, 11, 12, and 13). Common arterial sites requiring treatment include the descending genicular artery, inferior medial genicular artery, and inferior lateral genicular artery [9]. The mean number of vessels embolized per knee has ranged between 1.3 and 3.2 [9, 11, 12, 15]. It is important to note that arterial flow is preserved in the selected artery so as to minimize risks of ischemic complications. Injecting the minimum embolic volume necessary to clear the neovascularity in the area of symptoms is useful in achieving this goal while also minimizing post treatment pain symptoms.

Reported complications after GAE are typically minor and transient. The most frequent complication is skin mottling associated with transient cutaneous ischemia and occurs in approximately 25% of cases according to a meta-analysis [25]. This complication is thought to be mitigated by application of ice packs during the embolization. In one study, while 18% of subjects experienced focal skin necrosis secondary to non-target embolization, no additional skin complications were reported once icepacks began being applied in the procedure, as part of a protocol modification [11]. Other reported complications include transient peripheral neuropathy, which was reported to occur in up to 10% of patients in one study and puncture site hematoma which in rare instances required overnight admission for observation [11, 12]. No severe adverse events attributable to GAE have been reported [25]. However, to mitigate risk,

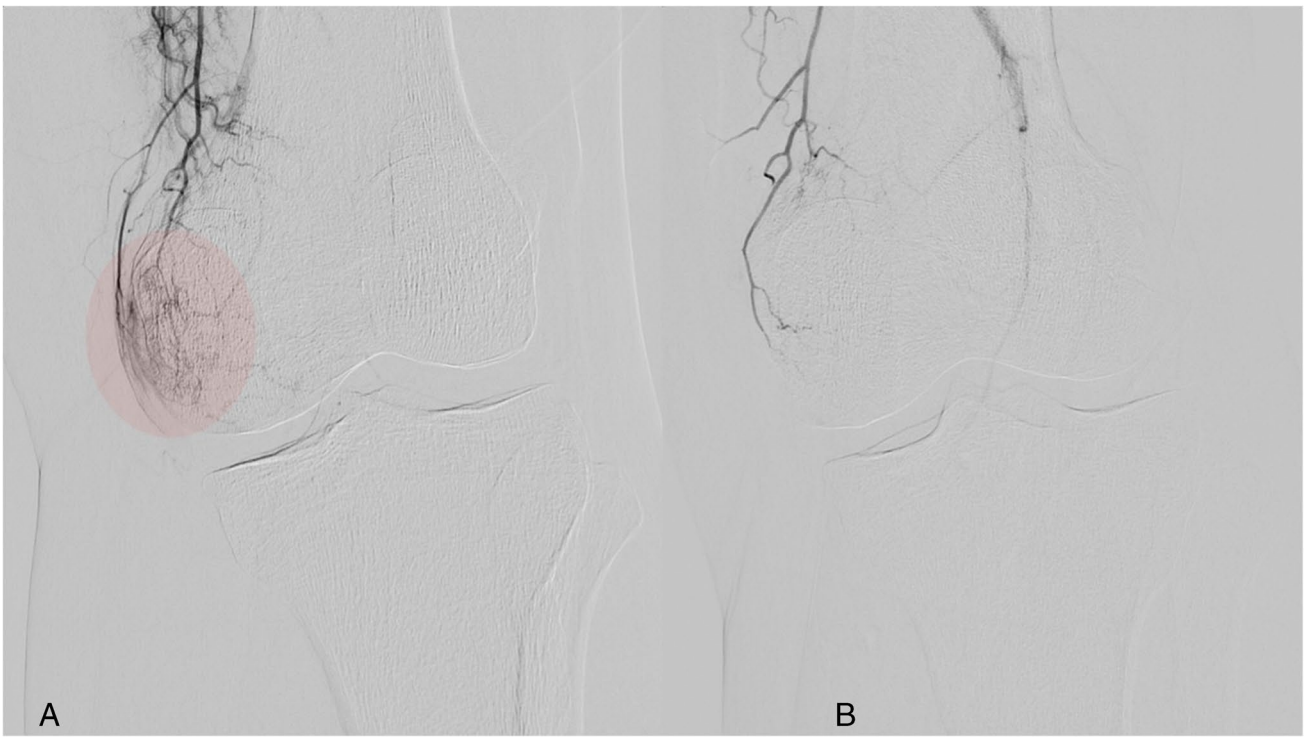

Fig. 9 **A** Descending genicular artery with distal neovascularity (highlighted in red oval). **B** Resolution of neovascularity following GAE

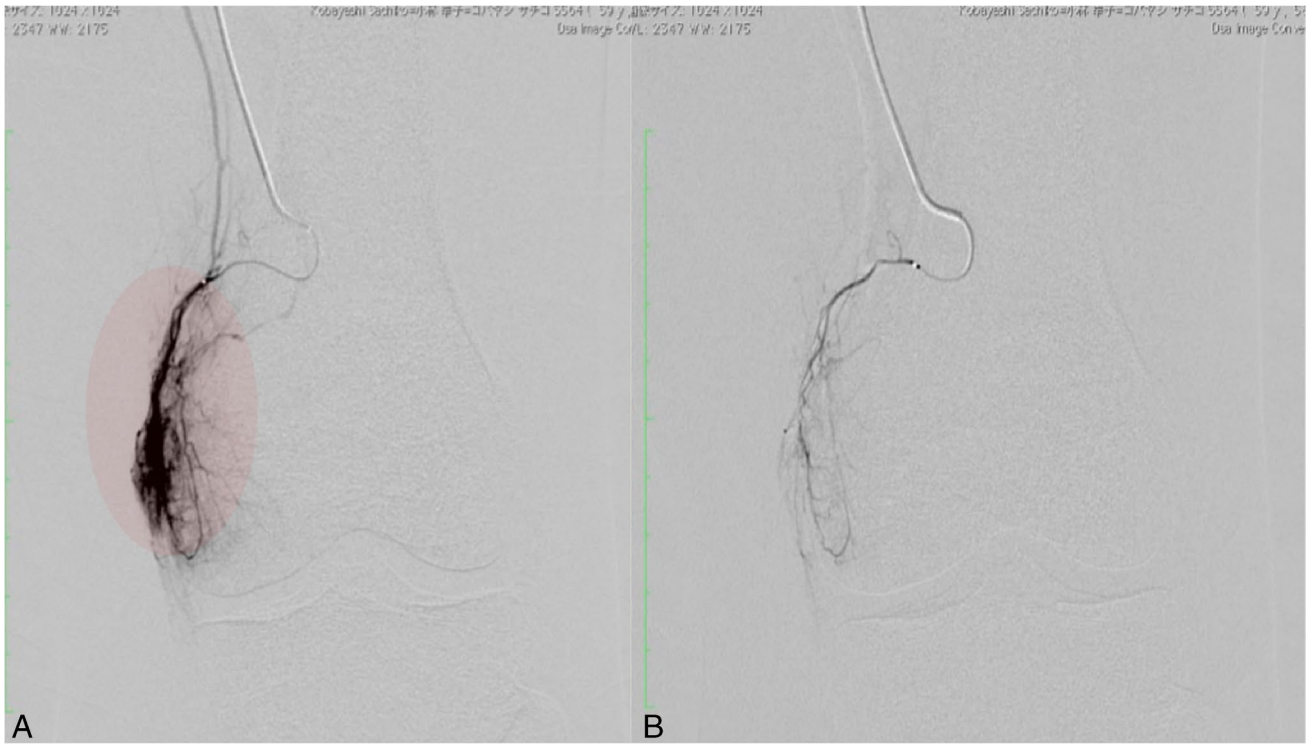

Fig. 10 **A** Superior medial genicular artery with neovascularity (highlighted in red oval). **B** Resolution of neovascularity following GAE

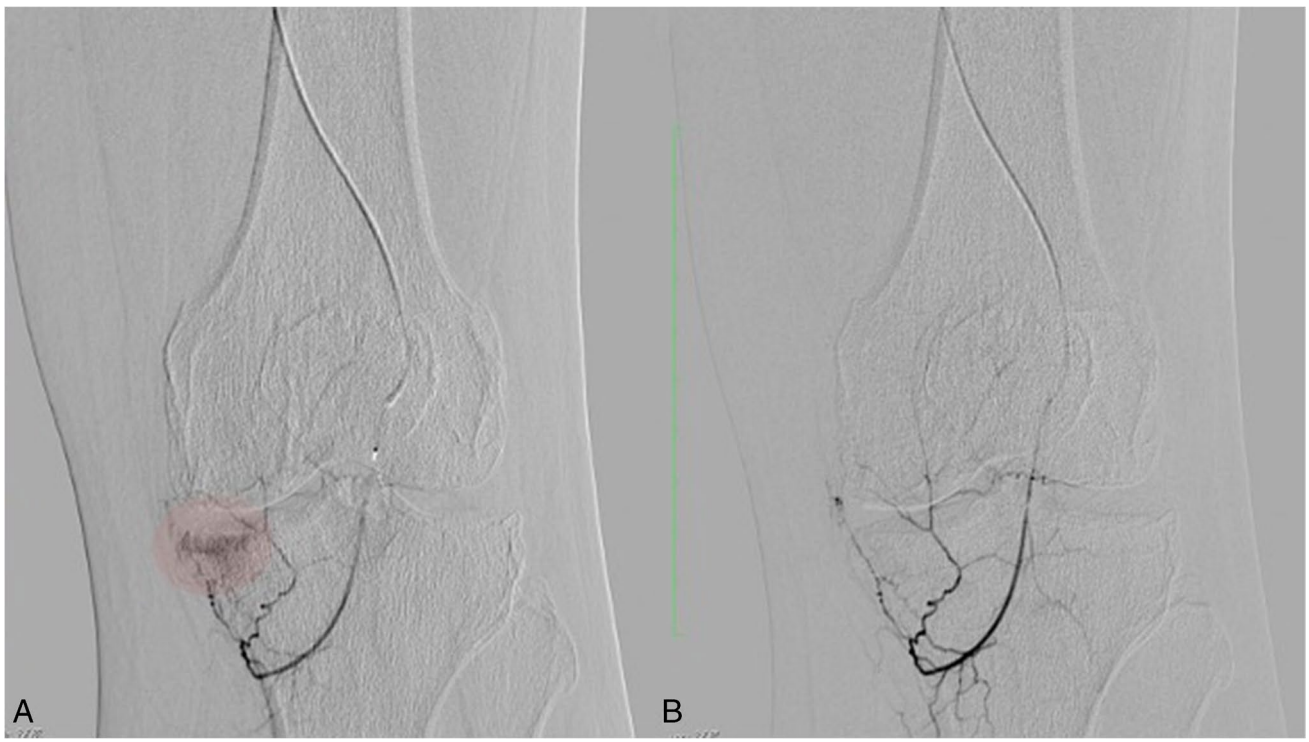

Fig. 11 **A** Inferior medial genicular artery with neovascularity (highlighted in red oval). **B** Resolution of neovascularity following GAE

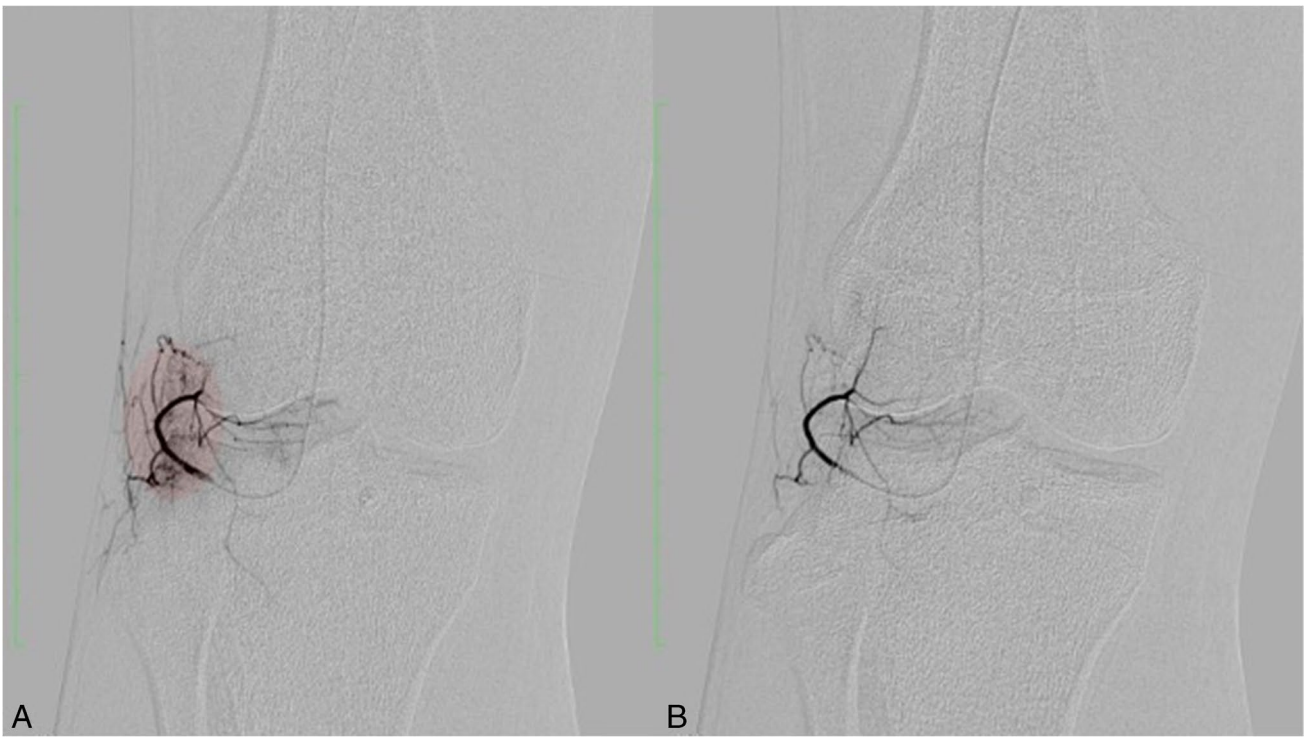

Fig. 12 **A** Inferior lateral genicular artery with neovascularity (highlighted in red oval). **B** Resolution of neovascularity following GAE

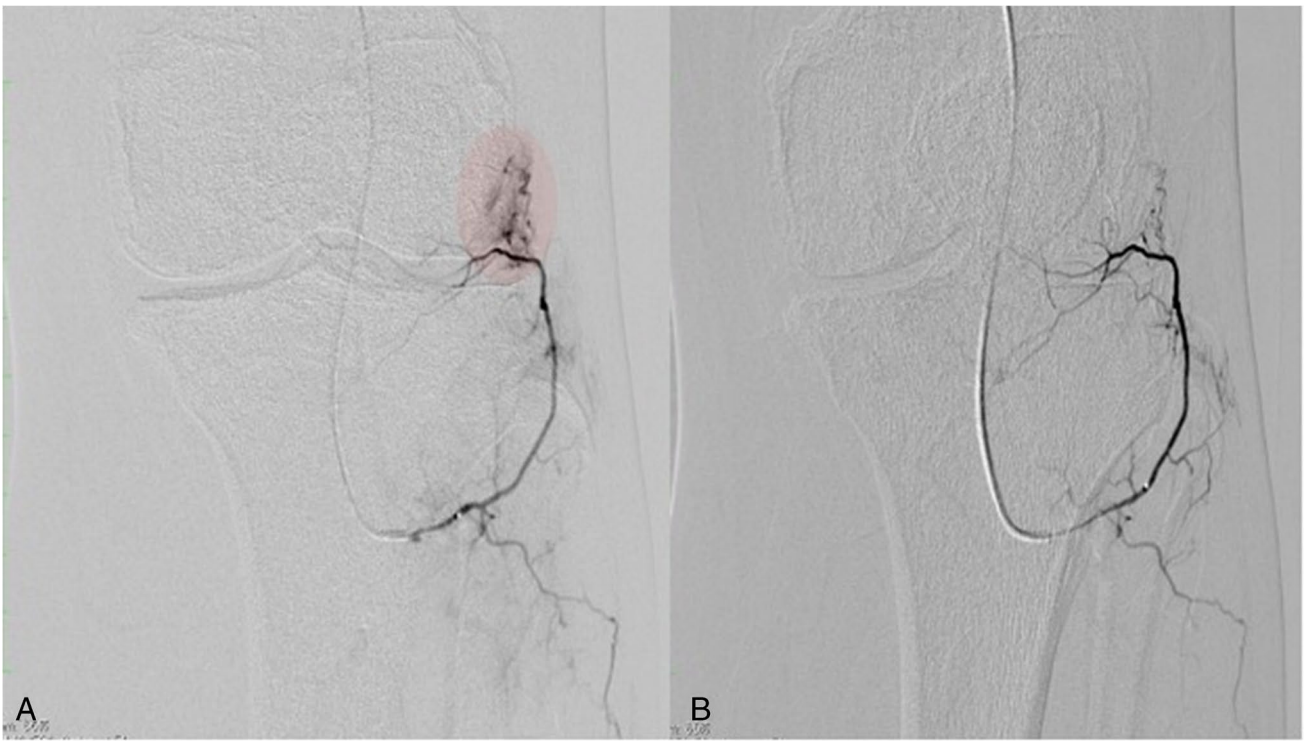

Fig. 13 **A** Anterior tibial recurrent artery with neovascularity (highlighted in red oval). **B** Resolution of neovascularity following GAE

patient selection is important as patients with significant atherosclerotic burden may be at greater risk of developing serious complications. Radiation exposure is relatively limited in GAE, with one study reporting a mean exposure of 100.2 mGy (range 16.9 mGy to 360 mGy) [13].

Outcomes of Genicular Artery Embolization

Recent studies have demonstrated clinical success in patients undergoing genicular artery embolization for the treatment of OA-related knee pain (Fig. 14). Two published studies by Okuno et al. highlighted initial findings regarding the intervention [8, 9]. The prospective trial in 2017 included 72 patients (KL grades 1–3) and had a maximum follow-up duration of 4 years. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to monitor outcomes. The WOMAC is a self-administered questionnaire used to evaluate patients with hip and knee OA. It consists of scales evaluating pain, stiffness, and physical function with an overall score of 0–96. Higher WOMAC scores indicated increased pain, increased stiffness, and diminished physical function. Clinical success was defined as a > 50% reduction in WOMAC pain scores at the time of follow-up and was observed in 86.3% and 79.8% of patients at 6 months and 3 years, respectively. Magnetic resonance imaging of the patients at the 2-year follow-up period also revealed improvements in synovitis and no significant difference in whole organ magnetic resonance imaging scores regarding cartilage, marrow abnormality, bone cysts, bone attrition, osteophytes, menisci, and ligaments (Fig. 15).

Since the publication of the studies by Okuno et al., additional works have been published showing similar success in demonstrating the role of GAE in treating OA-related knee pain [11–15]. Prospective trials by Bagla et al. and Landers et al. in 2020 included 20 and 10 patients respectively and showed response to GAE in terms of reduction in pain scores [12, 14]. In the study by Bagla et al., mean WOMAC scores improved from 61 ± 12 at baseline to 29 ± 27, and mean VAS pain scores improved from 76 mm ± 14 at baseline to 29 mm ± 27 at 6 months. These improvements were observed in 80% and 85% of patients reporting WOMAC and VAS scores respectively. Landers et al. defined a responder to treatment as 2 of 3 conditions: (1) pain improvement > 20% and change of > 10 on a 0–100 scale, (2) functional improvement of > 20% or 10-point improvement on the pain scale, and (3) patient's global assessment of moderately or much better pain symptoms. Using this threshold, their work demonstrated 60% of patients as responders to GAE at 12 months; however, only 30% were responders at 2 years [14]. The authors suggested that the lower response rate when compared to previous studies may be due to a larger population of obese patients in the observed cohort. Patient variables associated with treatment outcomes warrants further investigation.

Two prospective trials in 2021 by Little et al. and Padia et al. included 38 and 40 patients respectively and followed patients for a duration of 1 year [11, 15]. The visual analog scale (VAS) was used in the GENESIS trial by Little et al. This is a widely used pain scale either from 0 to 10 or 0 to 100 whereby 0 indicates no pain and the top end of the scale indicates severe pain. In this scoring system, the VAS is recorded by subjects making a mark on a line along the numerical continuum that represents no pain and worst pain at each end of the scale. The GENESIS trial demonstrated an improvement of VAS pain scores from 60 mm at baseline to 36 and 45 mm at 3 months and 1 year, respectively. Padia et al. defined clinical success as a 50% reduction in WOMAC score, similar to previously mentioned studies. In this cohort 68% achieved clinical success of 62.9% of which had a reduction of WOMAC score of > 75% at the 1-year follow-up. One

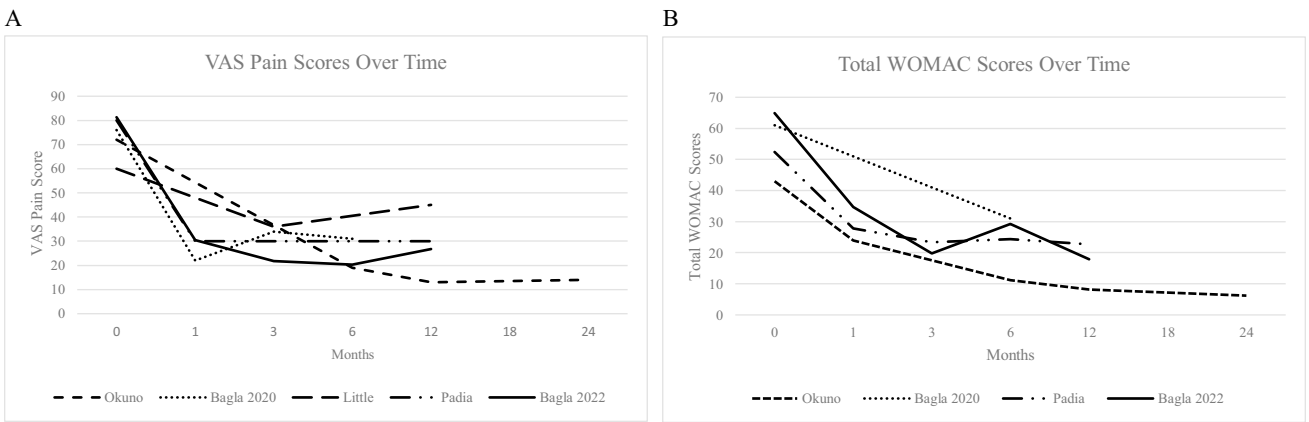

Fig. 14 **A** Change in VAS scores following GAE is demonstrated over time. **B** Change in total WOMAC scores following GAE is demonstrated over time

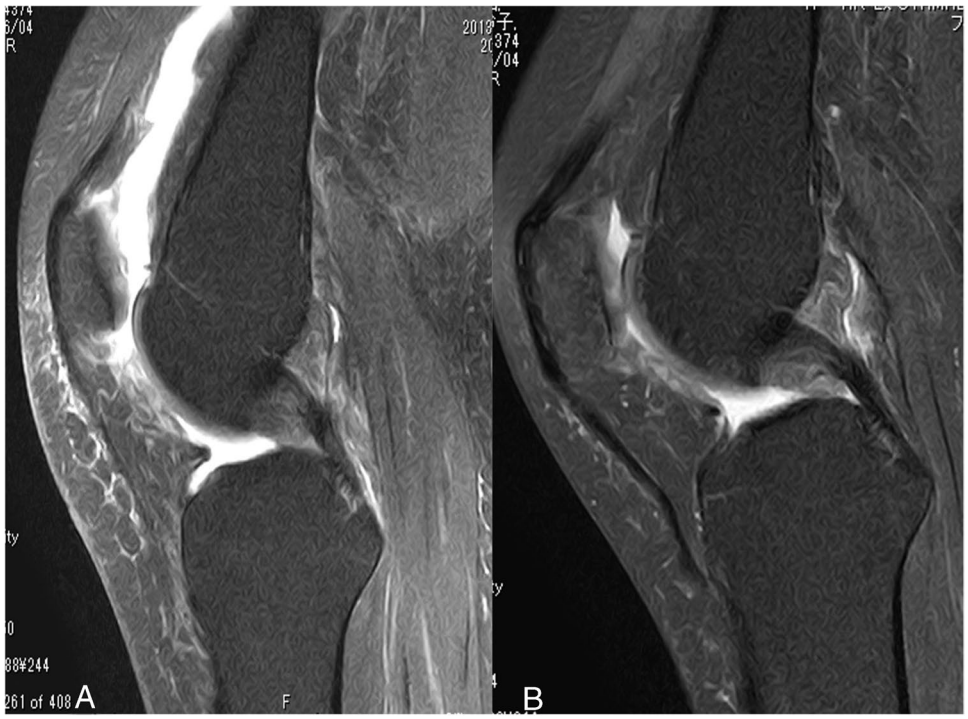

Fig. 15 **A** Pre-GAE knee MRI (T2 weighted) demonstrating synovial thickening and effusion. **B** Two years post GAE, knee MRI demonstrates reduced effusion volume and reduced synovial thickening

patient that had demonstrated clinical success at 3 months had pain recurrence at the 1-year time point.

A randomized-controlled trial by Bagla et al., published in 2022, included 21 patients that were randomized to a 2:1 ratio. Fourteen patients were randomized to the embolization arm and 7 to a sham arm [13]. Minimum clinically relevant improvement (MRCI) was defined as 16% for the total WOMAC and 12% for the VAS pain scores. All patients in the sham arm crossed over to the treatment arm after revealing no clinical response. At the 1-month follow-up, a response rate of 79% and 43% was observed in the treatment and crossover arms, respectively. The WOMAC scores from the treatment group continued to decrease from a 64.9 at baseline to 34.7, 19.8, 29.3, and 17.9 at 1, 3, 6, and 12 months respectively. VAS pain scores decreased as well from 81.3 at baseline to 30.5, 21.7, 20.3, and 26.7 at 1, 3, 6, and 12 months respectively. The crossover cohort demonstrated similar improvements in WOMAC from 65.9 at baseline to 46.3, 40.9, 26, and 16.3 at 1, 3, 6, and 12 months respectively.

Future directions

Currently, available data suggests that GAE is safe and effective in treating OA-related knee pain [25]. However, since OA therapies are susceptible to placebo effects, additional blinded trials have been recommended [26]. If these trials substantiate current data, they may facilitate greater acceptance of GAE among referring physicians and allow for the potential incorporation of GAE into pain management guidelines for OA.

Defining the ideal patient population likely to benefit from GAE is another area meriting further investigation. Gaps in knowledge exist regarding OA severity and GAE outcomes. A commonly used scale in GAE literature for assessing OA severity is the Kellgren and Lawrence (KL) classification. The scale radiographically grades OA on weightbearing images from 0 to 4, with 0 being no joint space narrowing or reactive changes and 4 being severe OA with large osteophytes and severe joint space narrowing. In one study, superior reductions in pain were reported for patients with mild to moderate OA (KL 1–3) compared to a small subset of patients with severe OA (KL-4) (10). It is hypothesized that patients with KL-4 OA have bone on bone impact and potential marrow edema contributing to persistent pain. Despite treating synovitis with GAE in this cohort, bone marrow edema may continue to contribute to knee pain [27]. Further investigation is necessary as subsequent literature did not reproduce these findings. In a study by Padia et al. of 40 patients, 16 (40%) had KL-4 disease, and a substantial difference in clinical outcomes between patients with KL-2 or KL-3 disease and those with KL-4 disease was not reported [11]. Along the spectrum of OA progression, a subset of patients who ultimately undergo TKA due to OA may also benefit from GAE research. It's reported that approximately 20% of patients continue to experience chronic knee pain following TKA [28]. With limited treatment options for chronic pain, evaluating

GAE in this population may also be considered. In addition, patients suffering from recurrent hemarthrosis following TKA can also be considered for GAE as it has been shown to be safe and effective in this population [16].

Prior studies have researched the presence of specific characteristics of knee OA prior to treatment [27, 29]. An imaging finding correlating with a substantially decreased response to GAE therapy was the presence of a full-thickness cartilage defect. Other findings such as effusion synovitis, high-grade osteophytes, bone marrow lesions, and subregional cartilage lesions (all associated with a higher KL grade) were associated with decreased pain improvement. These preliminary findings suggest that imaging may be useful in identifying patients who are less likely to respond to GAE. The role of advanced imaging such as dynamic contrast enhanced MRI may also offer further insight into the relationship between synovitis and OA phenotypes which are more likely to have treatment response [30–32].

Defining the ideal embolic agent would also benefit from further investigation. Currently, temporary and permanent particle embolics are used, and the most effective embolic has not clearly been defined. Opportunities exist for investigating the role of permanent and temporary liquid embolics, which may penetrate more deeply into the neo-vasculature. Furthermore, embolics which embolize the hypervascularity and elute medications to inhibit inflammation or angiogenesis may potentially provide even more effective and durable outcomes.

Finally, assessing the long-term outcomes of GAE as it pertains to OA progression is critical. Given the lack of disease modifying interventions for OA, understanding whether embolization slows down the process of hyperemia, inflammation, and OA progression would offer new insights and avenues for treatment of OA.

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Highlights

- *GAE is a superselective embolization of joint neovascularity in patients with OA and angiogenesis.*
- *Clinical trials suggest that GAE is safe and effective in treating OA-related knee pain refractory to conservative management.*
- *An understanding of genicular artery anatomy, technique, and literature is critical for optimizing outcomes and appropriately managing patient expectations.*