Genicular Artery Embolization for the Treatment of Knee Pain Secondary to Osteoarthritis

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ABSTRACT

Purpose: To evaluate the efficacy and safety of embolization of hyperemic synovial tissue for the treatment of knee pain secondary to osteoarthritis (OA).

Materials and Methods: Twenty patients with radiographic knee OA and moderate-to-severe pain refractory to conservative therapy were enrolled in a prospective, 2-site pilot study. Genicular artery embolization (GAE) was performed with 75- or 100-μm spherical particles. Patients were assessed with magnetic resonance imaging at baseline and at 1 month and with the Visual Analogue Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline and at 1, 3, and 6 months. Adverse events were recorded at all timepoints.

Results: Embolization of at least 1 genicular artery was achieved in 20/20 (100%) patients. Mean VAS improved from 76 mm ± 14 at baseline to 29 mm ± 27 at 6-month follow-up ($P < .01$). Mean WOMAC score improved from 61 ± 12 at baseline to 29 ± 27 at 6-month follow-up ($P < .01$). Self-limiting skin discoloration occurred in 13/20 (65%) patients. Two of 20 (10%) patients developed plantar sensory paresthesia that resolved within 14 days.

Conclusions: GAE to treat knee pain secondary to OA can be performed safely and demonstrates potential efficacy. Further randomized comparative studies are needed to determine true treatment effect versus placebo effect.

ABBREVIATIONS

GAE = Genicular artery embolization, MCID = minimal clinically important difference, OA = osteoarthritis, SD = standard deviation, STIR = short tau inversion recovery, VAS = Visual Analogue Scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index

Knee osteoarthritis (OA) affects more than 30 million Americans, with pain being the hallmark symptom. For patients not yet appropriate for total knee arthroplasty, medication and knee injections are the mainstays of therapy. However, chronic medication use has potential complications, including liver dysfunction, renal dysfunction, gastrointestinal ulceration, and opiate addiction. Furthermore, steroid and hyaluronic acid intra-articular injections demonstrate inconsistent efficacy and require repetitive treatment (1).

Although OA has traditionally been thought of as a degenerative disease related to chronic repetitive injury, it has been recently discovered that, in most patients, there is associated chronic inflammation (2). The inflammatory process leads to synovial angiogenesis through the release of cytokines such as vascular endothelial growth factor (3). Angiogenesis has been linked to the formation of osteophytes, cartilage breakdown, and an increase in knee pain (4,5).

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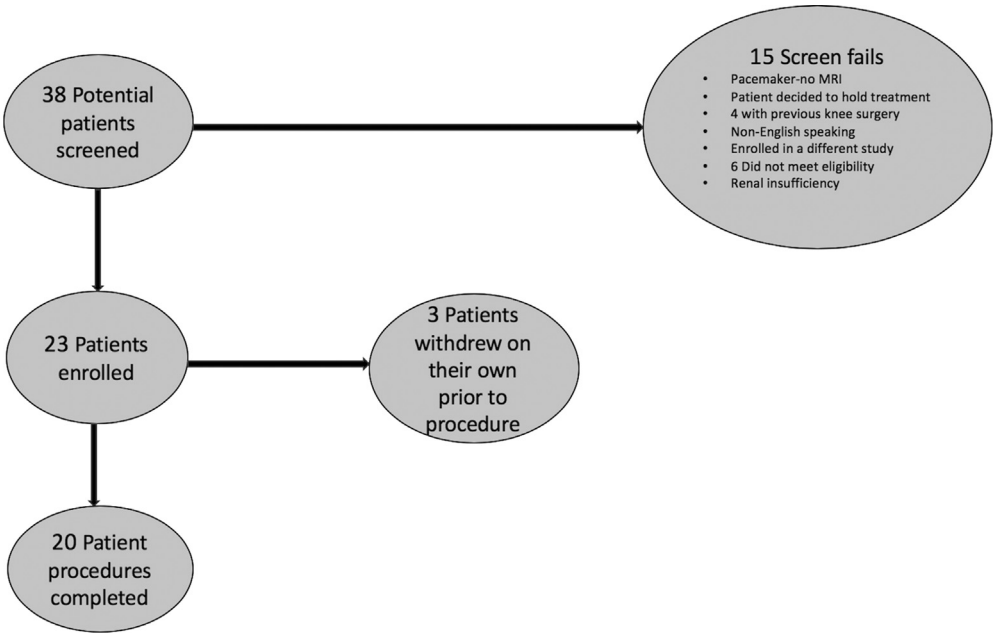

Figure 1. Flow chart demonstrating patient allocation.

Particulate embolization of the genicular arteries has been previously described as a safe and effective treatment in the setting of post-knee–arthroplasty hemarthrosis (6,7). In 2015, Okuno et al (8) described a similar technique for palliation of pain secondary to OA. Subsequent to their initial report, the same authors published a study with a larger sample size (72 patients, 95 knees) and mid-term clinical outcomes (follow-up to 36 months). The primary embolic agent used was a rapidly absorbable mixture of antibiotic agents (imipenem/cilastatin sodium). A permanent embolic was used only if the primary embolic was contraindicated due to allergy (7 procedures). They described an 80% clinical success rate at 3-year follow-up (9). The purpose of the present study was to evaluate the safety and clinical outcomes of genicular artery embolization (GAE) using a permanent embolic agent in a U.S. population.

MATERIALS AND METHODS

Regulatory oversight for this study (ClinicalTrials.gov NCT02850068) was provided by the institutional review board as well by an Investigational Device Exemption from the U.S. Food and Drug Administration. All study activities were in compliance with Health Insurance Portability and Accountability Act regulations. This prospective trial was conducted at 2 U.S. sites and enrolled 20 patients between January 2017 and January 2018 (**Fig. 1**). Patients presenting with osteoarthritic knee pain to orthopedic or interventional radiology clinics associated with the trial sites were evaluated for enrollment. Inclusion criteria included age 40 years or older; mild-to-moderate knee OA as determined by radiographs demonstrating Kellgren–Lawrence grade 1–3 findings; self-reported pain of at least 5/10; and failure of conservative therapy, such as pain medication or intra-articular injections, for at least 3 months. Patients were excluded if they had a history of rheumatoid arthritis, renal insufficiency, irreversible coagulopathy, previous arthroplasty, joint infection, or Kellgren–Lawrence grade 4 radiographic findings. All patients underwent evaluation with magnetic resonance imaging (MRI) before the procedure and at 1 month after GAE. MRI included multi-planar pre- and post-contrast T1-weighted images as well as multi-planar short tau inversion recovery (STIR) sequences. Pain, stiffness, and disability were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, which was completed by patients using a paper form. The WOMAC is a validated, disease-specific instrument for knee OA that consists of 24 items (global score range, 0–96): 5 regarding pain, 2 regarding stiffness, and 17 regarding physical function; score ranges for each subset of items are: pain, 0–20; stiffness, 0–8; and physical function, 0–68 (10). Patients were also asked to report the degree of pain in their affected knee using a 100-mm Visual Analogue Scale (VAS) at baseline, 1 month, 3 months, and 6 months after GAE.

The study cohort ranged in age from 49 to 84 years (mean, 59.4 years) and included 9 males and 11 females. On the basis of body mass index (BMI), 2 patients were considered obese (30–34 kg/m^2) and 10 were considered morbidly obese (35 kg/m^2 and higher). Mean BMI for the group was 35 kg/m^2. Radiographs revealed moderate OA in 18 patients (Kellgren–Lawrence grade 2 or 3) and mild changes in 2 patients (Kellgren–Lawrence grade 1) (**Table 1**.) Baseline pain management included analgesics alone for 9 patients, analgesics and intra-articular injections for 9 patients, and intra-articular injections alone for 2 patients.

Procedures were performed by interventional radiologists with 8, 5, and 5 years of experience performing

Table 1. Individual Patient Baseline Data

Patient	Age (years)	Gender	BMI (kg/m^2)	Knee Laterality	Kellgren–Lawrence Class	WOMAC Score	Baseline VAS Pain Score
1	65	M	37.75	Right	3	50	58
2	67	M	29.52	Right	3	36	64.8
3	54	M	33.07	Right	3	48	67
4	54	F	37.31	Right	2	61	54
5	70	F	47.45	Right	2	72	71
6	56	F	50.92	Right	3	75	91
7	49	F	42.89	Left	2	63	83
8	63	F	29.75	Left	3	86	100
9	62	M	50.20	Left	3	67	80
10	61	F	37.44	Left	2	69	100
11	64	M	29.43	Right	3	65	87
12	70	F	44.62	Left	1	76	74
13	84	M	21.71	Left	3	51	76
14	75	M	23.01	Left	1	49	79
15	52	F	32.26	Left	2	58	69
16	64	M	25.09	Right	2	52	67
17	66	M	23.19	Right	3	68	71
18	65	F	28.24	Right	2	54	56
19	51	F	35.51	Right	2	64	75
20	49	F	41.27	Left	2	50	100

BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = Visual Analogue Scale.

embolization procedures. Patients were evaluated before the procedure to determine the region of the knee that was most painful. The procedure was performed under moderate sedation with midazolam (West-ward, Eatontown, New Jersey) and fentanyl (Hospira, Lake Forest, Illinois) and local anesthesia at the arterial puncture site. Arterial access was gained to the contralateral femoral artery with a 6-Fr sheath. Lower extremity digital subtraction angiography was performed of the distal superficial femoral artery to identify the target genicular arteries in the region of maximal pain (Fig. 2). A 2.4-Fr microcatheter (j-shape angled Direxion; Boston Scientific, Natick, Massachusetts) was used to catheterize the genicular arteries, and angiography was performed to identify a "tumor blush" pattern of opacity (Fig. 3). Embolization was performed with either 75- or 100-μm spherical particles (Embozene; Boston Scientific). To create a dilute embolic solution, 9 ml of contrast material were added to the 6 ml of particles in solution that came in the pre-packaged syringe. The embolization technique involved injecting 0.2-ml aliquots of embolic solution followed by digital subtraction angiography after each injection. This was continued until the "tumor blush" was no longer evident (Fig. 4). All of the genicular arteries supplying the region of maximal tenderness were interrogated and embolized in this manner if "tumor blush" was seen on angiography. Patients were discharged on the same day. Assessment for adverse events (AEs) was performed in person and/or by telephone at 1 day after the procedure and at all follow-up intervals. All follow-up evaluation was performed by research personnel and not the operators themselves, to avoid bias. If AEs were reported, evaluation was then performed by the operators to determine severity and if treatment was warranted.

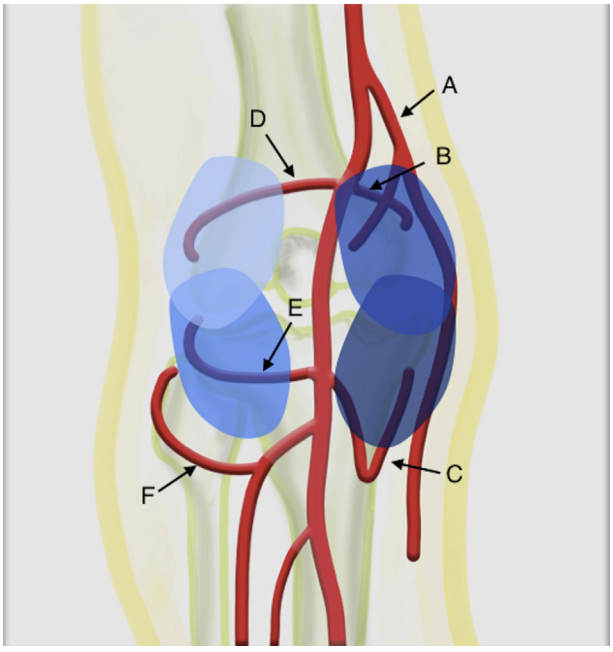

Figure 2. Illustration depicting the typical branching patterns of the genicular arteries. Shaded blue circles represent regions of pain that may correspond to those arteries supplying the respective synovial tissue. (**a**) Descending genicular artery; (**b**) superior medial genicular artery; (**c**) inferior medial genicular artery; (**d**) superior lateral genicular artery; (**e**) inferior lateral genicular artery; and (**f**) recurrent genicular artery.

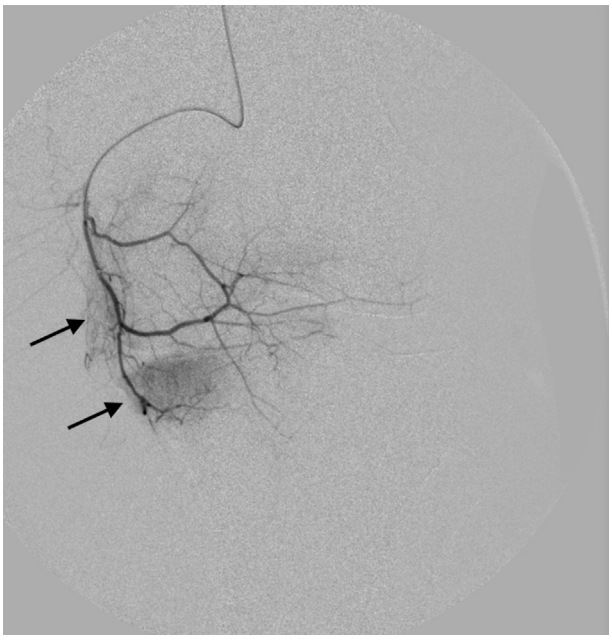

Figure 3. Angiography of the branches of the superior medial genicular artery shows hypervascular "blush" (arrow) over the medial inferior aspect of the knee.

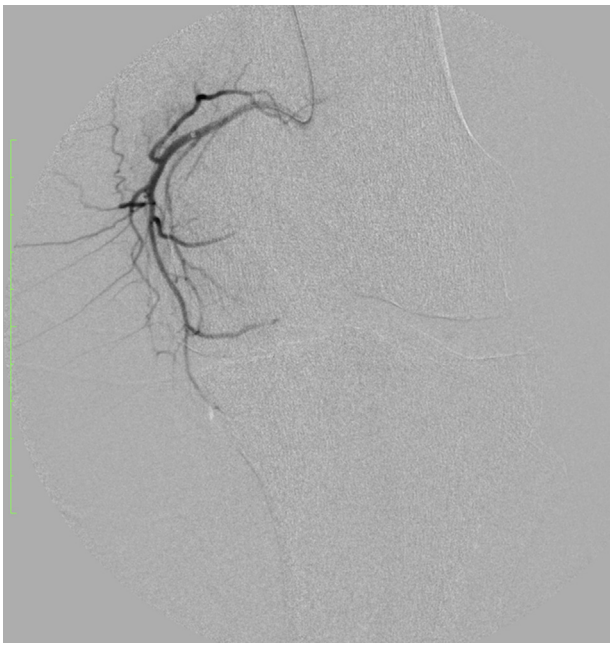

Figure 4. Angiography after embolization depicts the end point of "pruning" of the hypervascular synovium. The parent genicular artery remains patent.

Technical success was defined as selective catheterization and embolization of at least 1 genicular artery. Clinical success was defined as a change in VAS or WOMAC of 20% and 16% at 6 months, respectively, without an increase in baseline incidence of pain medication use or intra-articular injection. This was based on the minimal clinically important difference (MCID) (11,12) that can be discerned by the aforementioned scales. The incidence of medication use and/or intra-articular injection to treat knee pain was recorded at every follow-up visit. MRI assessment was performed before GAE and at 1 month after embolization. AEs were reported according to the Society of Interventional Radiology classification schema (13).

Statistical Analysis

The study was powered to detect an MCID in WOMAC total score of 16% and VAS of 20% at 6 months (11,12). At the time of the current study's development, only 1 prior study had examined the use of transcatheter arterial embolization for the treatment of knee pain secondary to OA (9). In that study, the baseline WOMAC total score (mean ± standard deviation [SD]) was 48.5 ± 9.4 (8). The primary outcome of that study was a 16% reduction in the baseline WOMAC total score. Using the baseline total score from that study, a sample size of 15 was determined to have an 80% power under a matched-pairs *t*-test analytic strategy to detect a 16% difference (7.8 points) in means, assuming an SD of 10 points and a conservatively low correlation of baseline and 6-month scores of .5 (G Power, version 3.1.9.2). To prevent inadequate power after a potential lost-to-follow–up rate of 30%, 20 total patients were enrolled. This sample size also had adequate power to detect the secondary outcome: a reduction in the VAS by 20% at 6 months of follow-up.

This was a pre-post analytical design, and the primary statistical method was a paired *t*-test, examining changes from baseline to 6 months. Normality for the difference of the VAS baseline and 6-month score and the difference of the WOMAC baseline and 6-month score was tested using the Kolmogorov–Smirnov test. Although the small sample size precludes definitive conclusions using this method unless large departures from normality exist, *P* values were $> .15$ for both differences, indicating no evidence against violation of normality. This test was supplemented with subjective evaluations of stem-and-leaf and Q-Q plots. No plots suggested egregious departures from normality.

Frequencies, including pre-post change, were reported as percentages with 95% confidence intervals (CIs). Continuous data were reported as means with 95% CIs. *P* values less than or equal to .05 indicated statistical significance. All analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

For the 20 embolization procedures performed, 75-μm Embozene was used for the first 9 patients, and 100-μm particles were used for the subsequent 11 patients. The mean number of arteries embolized per patient was 2.5 (SD, 0.9). All patients demonstrated abnormal synovial hypervascularity in the area of maximal knee pain. Mean procedure time was 81 minutes (SD, 31 minutes), with a mean fluoroscopy time of 29 minutes (SD, 12 minutes) and

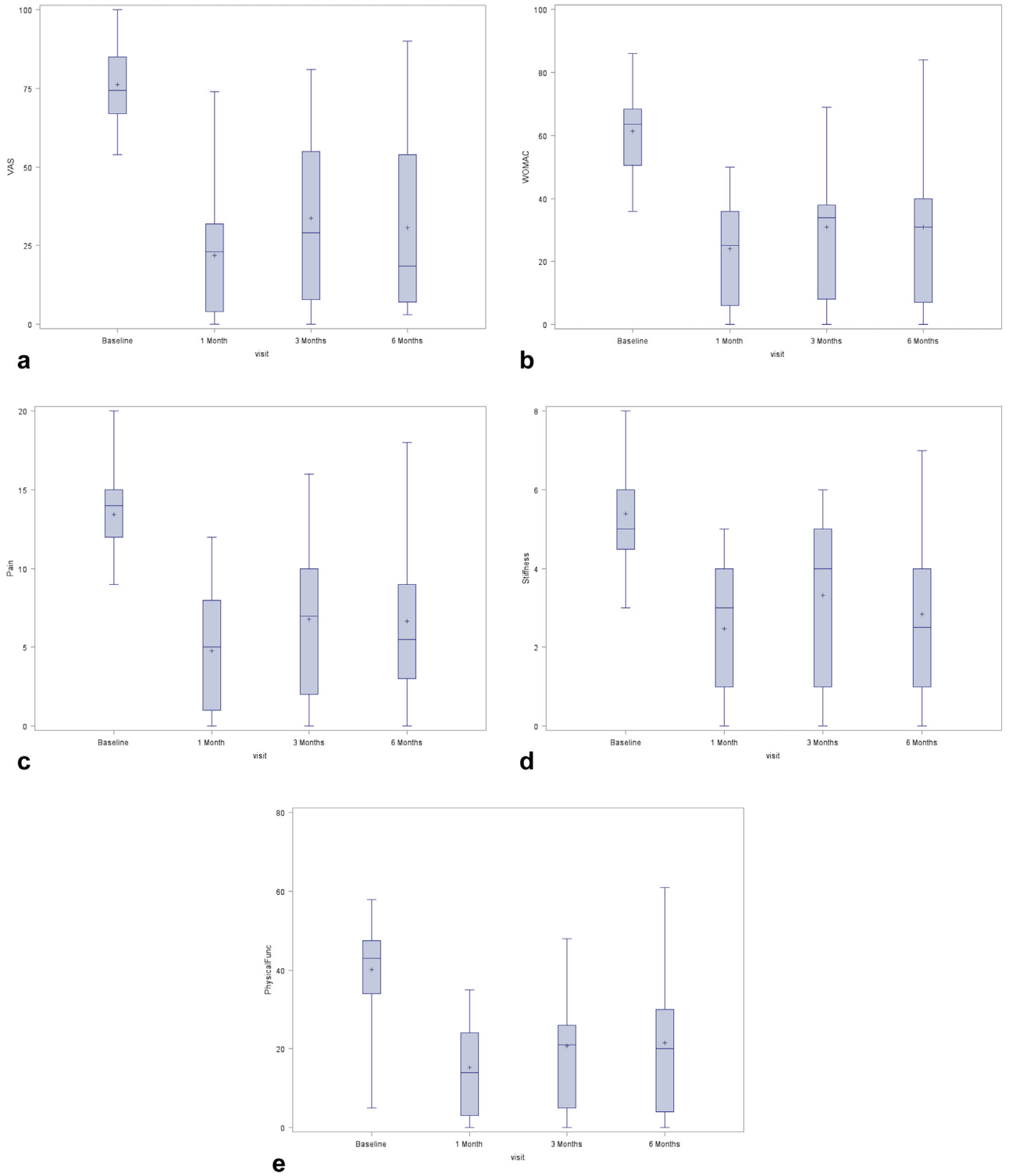

Figure 5. Box plots depicting longitudinal changes in symptom metrics: (**a**) VAS, (**b**) total WOMAC score, (**c**) WOMAC pain score, (**d**) WOMAC stiffness score, and (**e**) WOMAC physical function score.

administered reference air kerma of 128 mGy (SD, 106 mGy). One patient was lost to follow-up for the 1- and 3-month intervals but presented for 6-month follow-up.

The mean VAS at baseline was 76 mm (SD, 14; 95% CI, 70–83) with a decrease to 22 mm (SD, 19; 95% CI, 13–31) at 1 month; 34 mm (SD, 26; 95% CI, 21–46) at 3 months; and 31 mm (SD, 28; 95% CI, 17–45) at 6 months. WOMAC score also decreased from 61 (SD, 12; 95% CI, 56–67) at baseline to 24 (SD, 17; 95% CI, 16–32) at 1 month; 31 (SD, 21; 95% CI, 21–41) at 3 months; and 31 (SD, 26; 95% CI, 18–44) at 6 months. The mean decrease between baseline and 6 months was 44 for VAS (SD, 30; 95% CI, 29–59) and

Table 2. Patients Taking Various Classes of Pain Medication at Baseline versus 6-Month Follow-Up

	Baseline	Six-Month Follow-up
Opiates	6	1
Acetaminophen	4	2
NSAIDs	13	6

NSAID = nonsteroidal anti-inflammatory drug.

31 for WOMAC (SD, 23; 95% CI, 19–42). Both decreases were significant ($P < .0001$). Longitudinal changes of VAS, total WOMAC score, and the sub-scores comprising the WOMAC score are depicted in Figure 5. No patients increased their baseline pain medication regimens during the study period. At 1 month, 100% of patients met the primary endpoint of an MCID in WOMAC score, and 95% (95% CI, 75%–100%) noted an MCID in VAS score. At 6 months, 80% (95% CI, 56%–94%) noted an MCID in WOMAC and 85% (95% CI, 62%–97%) noted an MCID in VAS. Sixty-five percent of patients (95% CI, 41%–85%) reported a decrease in daily analgesic medication use (Table 2).

Two patients had small regions (<2 cm) of increased STIR signal within the marrow of their femurs on follow-up MRI. These were interpreted as nonspecific foci of inflammation without the typical imaging characteristics of infection or infarction. No further imaging was obtained for these 2 patients because they did not report symptoms associated with these imaging findings.

AEs attributed to the procedure included skin discoloration (Fig. 6) without ulcer that resolved by the 3-month follow-up evaluation without intervention (n = 13, 65%); small access site hematoma (n = 1, 5%); and great toe plantar numbness that resolved within 2 weeks (n = 2, 10%). All AEs were classified as class A except for the great toe numbness, which was treated with gabapentin for 2 weeks, and was, therefore, a class B complication.

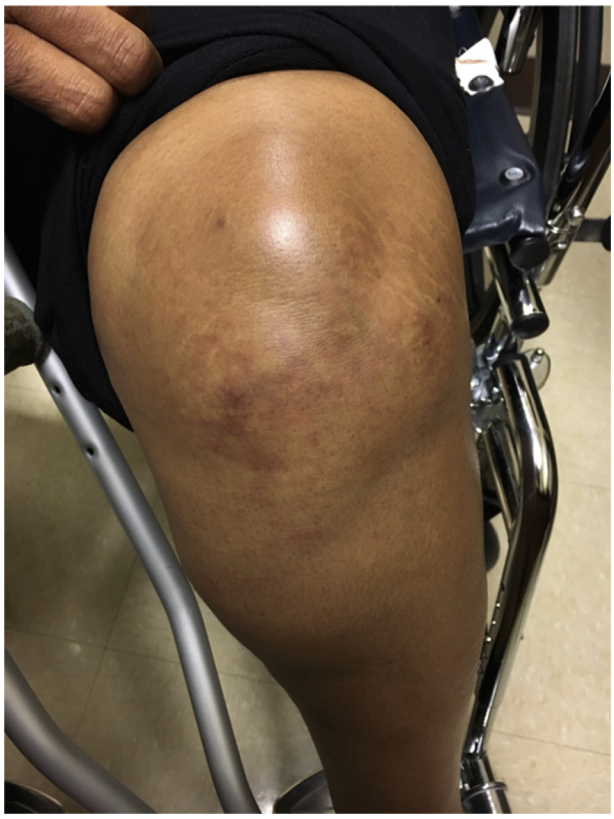

Figure 6. Photograph of leg 24 hours after embolization depicts the patchy areas of purpura that correspond to areas of transient cutaneous ischemia that were seen in 14 of 20 patients.

DISCUSSION

This study showed that most patients experienced a rapid decrease in pain and disability after GAE in the setting of knee OA. Nearly all patients demonstrated clinical improvement as measured by the VAS (95%) and WOMAC (100%) at 1 month. This was durable at 6 months in 85% and 80% of patients as demonstrated by VAS and WOMAC improvements, respectively. Although the MCID is defined as a reduction in VAS and WOMAC scores of 15% and 20% respectively, the actual mean improvements in this cohort exceeded these benchmarks at 62% and 52%, respectively.

The complications observed in this study population were thought to be due to nontarget embolization. First, the skin discoloration was likely a result of embolic particles occluding small cutaneous arterial branches. This occurred despite great care by the operators to position the microcatheters as selectively as possible and avoid reflux. Second, cases of plantar paresthesia were thought to be due to nontarget embolization of the medial plantar nerve, a branch of the tibial nerve that receives its vascular supply from branches of the popliteal artery (14). After neurologic symptoms developed in 2 patients, the decision was made to change to larger embolic particles (100 μm) for the remainder of the study. The hypothesis was that these particles would be too large to travel distal enough to result in nerve ischemia. After the change, no further post-procedural neurologic changes were seen.

Angiographic hypervascularity was seen in the region of maximal knee pain in all patients in this study, as it was in the prior investigation by Okuno et al (9). On the basis of arthroscopic findings, neovascularity has been associated with the inflammatory-mediated progression of articular cartilage degeneration in the setting of OA (4,5). Given this background, there is reason to suspect that embolization of the neovascularity resulting in a disruption of the inflammatory cycle could delay the progression of OA. However, investigation of this hypothesis would require long-term evaluation in comparative cohorts.

In contrast to the previously reported Japanese study, the current investigation was performed only with a permanent embolic agent. Okuno et al used imipenem/cilastatin sodium (Primaxin; Merck, Whitehouse Station, New Jersey), an antibiotic that crystallizes in solution and acts as a temporary embolic agent (9). Although widely used in some parts

of Asia, imipenem/cilastatin sodium is not available for embolization in the United States. In addition, patients may be allergic to imipenem/cilastatin sodium, warranting the investigation of other embolics for this purpose. Additionally, the current study's cohort differed from the initial Japanese experience in terms of obesity. The present study group had an average BMI of 35 kg/m^2, whereas the previous study's mean BMI was 25 mg/m^2. Despite this difference, the current study resulted in similar pain and disability reduction.

The primary limitation of this study was the lack of a control arm to determine how much of the observed effect was due to placebo effect. It is impossible to make any conclusions about the true efficacy of pain therapies without this determination. Also, the cohort size was small with heterogeneous radiographic findings. Because of the small number of patients, sub-analyses to determine optimal patient selection were not possible. Additionally, the study period was not long enough to determine the durability of GAE in this study population. The length of efficacy will be particularly important to understand when evaluating GAE from a cost perspective. Finally, long-term follow-up of the 2 patients with focal bone marrow edema on MRI was not performed. However, they had no symptoms that correlated with the imaging findings.

In conclusion, transcatheter arterial embolization is a safe treatment option for pain secondary to knee OA, with the potential to reduce pain and disability in the short term, even when performed with permanent embolic particles in an obese patient population. However, no conclusions can be made about the true efficacy of GAE without further evaluation that includes randomization to treatment or placebo.

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