Midterm Clinical Outcomes and MR Imaging Changes after Transcatheter Arterial Embolization as a Treatment for Mild to Moderate Radiographic Knee Osteoarthritis Resistant to Conservative Treatment

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ABSTRACT

Purpose: To describe the safety and efficacy of transcatheter arterial embolization for mild to moderate radiographic knee osteoarthritis (OA) that is resistant to conservative treatment.

Materials and Methods: This prospective study included 72 patients (95 knees) with OA of Kellgren–Lawrence (KL) grade 1–3 and persisting moderate to severe pain that was resistant to conservative management who were treated with transcatheter arterial embolization between July 2012 and March 2016. Clinical outcomes were evaluated at 1, 4, and 6 months and then every 6 months for a maximum of 4 years. The Whole-Organ Magnetic Resonance Imaging Score (WORMS) was evaluated at baseline and at 2 years after embolization in 35 knees.

Results: Abnormal neovessels were identified in all cases. There were no major adverse events related to the procedures. Mean Western Ontario and McMaster Universities Osteoarthritis Index pain scores significantly decreased from baseline to 1, 4, 6, 12, and 24 months after treatment (12.1 vs 6.2, 4.4, 3.7, 3.0, and 2.6; all $P < .001$). The cumulative clinical success rates at 6 months and 3 years after embolization were 86.3% (95% confidence interval [CI], 78%–92%) and 79.8% (95% CI, 69%–87%), respectively. WORMS scores at 2 years after embolization in 35 knees showed significant improvement of synovitis vs baseline ($P = .0016$) and no osteonecrosis or other evidence indicating aggressive progression of degenerative changes.

Conclusions: Transcatheter arterial embolization significantly improved pain symptoms and clinical function in patients with mild to moderate knee OA that was resistant to conservative treatment.

ABBREVIATIONS

CI = confidence interval, IPM/CS = imipenem/cilastatin sodium, KL = Kellgren–Lawrence [grade], OA = osteoarthritis, VAS = visual analog scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, WORMS = Whole-Organ Magnetic Resonance Imaging Scoring

Osteoarthritis (OA) is the most common degenerative joint disease and a leading cause of chronic pain and physical disability in older individuals (1). The lifetime risks of developing symptomatic knee OA are estimated at 40% in men and 47% in women (2).

The hallmark symptom of OA is pain. This is the symptom that drives individuals to seek medical attention and contributes to functional limitation and reduced quality of life (3,4); the alleviation of pain is the main motivation for treatment, including nonpharmacologic, pharmacologic,

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and surgical approaches. Severe and end-stage knee OA is successfully treated with joint replacement surgery, but effective management of mild to moderate radiographic knee OA refractory to conservative treatment can be difficult.

Although OA was viewed as a "wear-and-tear" disease for many decades, it is now generally accepted to be a low-grade inflammatory disease of synovial joints and a biomechanical whole-organ disease (5,6). Angiogenesis is believed to contribute to the genesis of inflammation and particularly to its maintenance (7). The new increased vascular network provides inflammatory cells access to the synovium and other joint tissues and promotes additional hyperplasia and inflammation in other vessels, leading to bone and cartilage destruction (8). In addition, studies on OA have shown that angiogenesis may contribute to chronic pain by enabling the growth of new unmyelinated sensory nerves along their path (9,10).

We have previously reported our early experiences with transcatheter arterial embolization in patients with mild radiographic knee OA that is refractory to conservative treatment (11). However, the mid- to long-term outcomes and complications could not be meaningfully assessed in the previous study because of the small number of patients and the short duration of follow-up.

The purpose of the present study was to evaluate the midterm clinical outcomes of transcatheter arterial embolization in patients with mild to moderate radiographic knee OA that is resistant to conservative management.

MATERIALS AND METHODS

This is a prospective, single-center, single-arm study including 72 patients and 95 knees with mild to moderate knee OA that is resistant to conservative treatment. A summary of baseline patient characteristics is provided in **Table 1**. All 14 patients described in our previous short-term study (11) were also included in the present study. Our institutional review board approved this prospective study, and all patients provided informed consent for the transcatheter arterial embolization procedure.

Inclusion criteria were as follows: presence of knee pain, Kellgren–Lawrence (KL) grade 1–3 assessed by routine weight-bearing knee radiographs, local tenderness around the knee, patient age 40–80 years, 3 months or more of conservative therapies (including oral nonsteroidal antiinflammatory drugs, oral opioid agents, physical therapy, stretching, muscle strengthening, or intraarticular injection of hyaluronic acid), and persistent moderate to severe knee pain (visual analog scale [VAS] score > 50 mm). All patients underwent magnetic resonance (MR) imaging, and those with osteonecrosis were excluded. Other exclusion criteria were local infection, malignancy, advanced atherosclerosis, rheumatoid arthritis, and previous knee surgery.

Table 1. Baseline Patient Characteristics

Variable	Value
Age (y)	64.4 (44–79)
Sex	
Male	23
Female	49
Pain duration (mo)	29.7 (4–180)
Affected side	
Right	49
Left	46
KL grade	
1/2	62
3	33
BMI (kg/m^2)	25.1 (19.3–40.7)
Baseline evaluation	
Pain WOMAC	12.1 (6–15)
Total WOMAC	42.5 (22–56)
Pain VAS (mm)	72 (54–100)

Note–Values presented as mean (range) where applicable. BMI = body mass index; KL = Kellgren–Lawrence; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Procedures

The distribution of local tenderness (indicating the presence of inflammation) was evaluated in all cases immediately before transcatheter arterial embolization and subdivided into eight areas (**Fig 1**) to determine the key arteries to be treated. Under local anesthesia, percutaneous arterial access was obtained by using a 3-F introducer sheath (Super Sheath; Medikit, Tokyo, Japan). The femoral artery was punctured in an ipsilateral anterograde fashion under ultrasound guidance in all cases. After intravenous administration of 2,000 IU heparin, a 3-F angiographic catheter (Judkins Right 2.5; Medikit) was introduced toward the popliteal artery. Digital subtraction angiography was then performed by manually injecting 3–5 mL of iodinated contrast medium (Hexabrix; Terumo, Tokyo, Japan). Selective angiography of the arteries (**Fig 1**) was performed by manual injection of 3 mL of contrast medium at a rate of 1 mL/s, with the 3-F angiographic catheter tip located at the origin of each artery. Abnormal vessels appeared as tumor blush–type enhancement in the arterial phase, often accompanied by early venous drainage. After the abnormal vessels were identified, embolic material was infused as described later. The catheter tip was positioned at the origin of the target arteries (ie, the same position previously used for diagnostic angiography); in some cases, more selective catheterization was performed by using a 1.7-F microcatheter (ASAHI Veloute; Asahi Intecc, Nagoya, Japan) to reach distal arteries while avoiding branches that did not feed abnormal vessels. Imipenem/cilastatin sodium (IPM/CS; Primaxin; Merck, Whitehouse Station, New Jersey) was used as the embolic material in 88 knees in 65 patients. Patients who had contraindications to IPM/CS (ie, a history of hypersensitivity or allergy to antibiotic agents or treatment with valproic acid) were treated with 75-μm Embozene microspheres instead (n = 7 knees in seven patients).

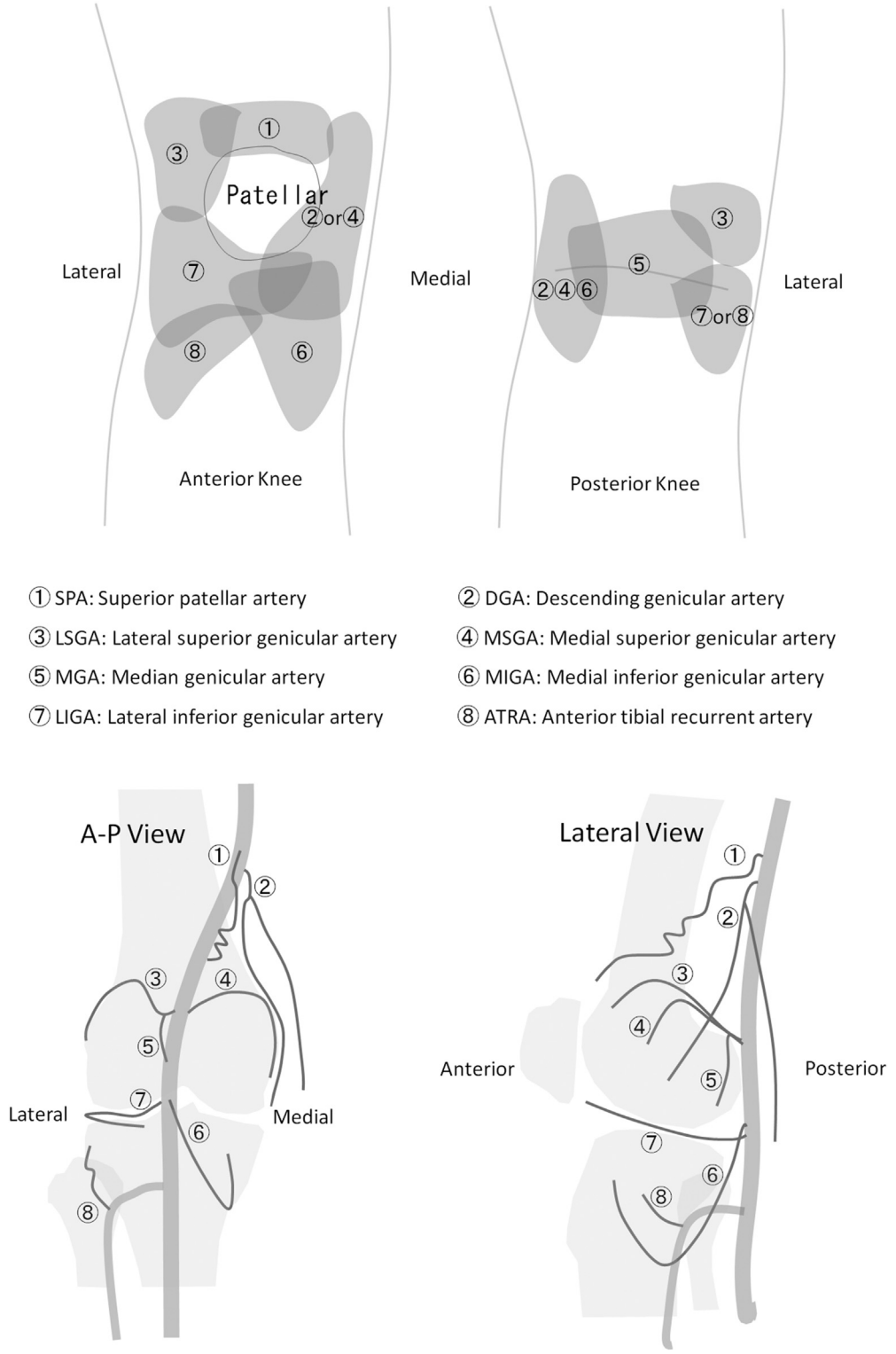

Figure 1. Anatomic distribution of arteries feeding the knee joint.

IPM/CS was selected based on previous reports (11,12); it is a crystalline compound that is slightly soluble in water and forms small-sized particles with an embolic effect when it is suspended in contrast agent. Therefore, a suspension of 0.5 g IPM/CS in 5–10 mL iodinated contrast agent was prepared by pumping syringes for 10 seconds and then injected in 0.2-mL increments. The 75-μm Embozene microspheres were administered in a similar manner: 0.2 mL of the Embozene solution was diluted in 2 mL of contrast agent and injected in 0.2-mL increments. The embolization endpoint was suppression or reduction in the filling of (and therefore blood flow in) abnormal vessels visible on

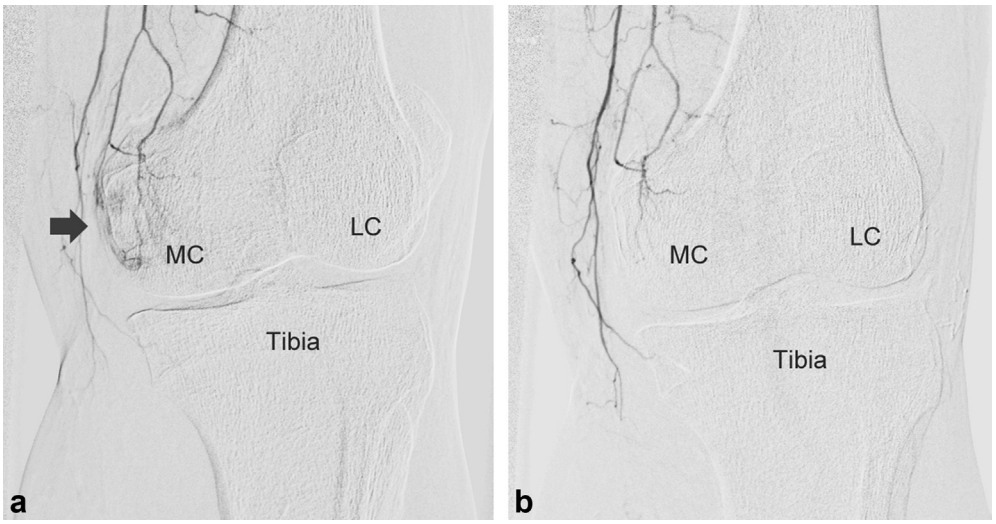

Figure 2. Angiographic findings before and after transcatheter arterial microembolization in a 69-year-old patient treated with IPM/CS. **(a)** Selective angiography from the descending genicular artery before embolization shows abnormal neovessels (arrow) adjacent to the medial condyle (*MC*). (LC = lateral condyle.) **(b)** Postembolization angiography shows elimination of hypervascularity.

angiography. Figure 2 shows examples of digital subtraction angiography images. We asked patients about their pain level to confirm the decrease in local tenderness several minutes after infusion of the embolic material. The catheter was removed after confirming successful reduction of the number of abnormal vessels on angiography and reduction of local tenderness by palpation. Hemostasis was achieved by manual compression. The patients were discharged on the same day.

Patients were advised to restrict activity to light household or office duties for 2 weeks and were allowed to continue previous conservative therapies. A second transcatheter arterial embolization procedure was considered if pain persisted or relapsed within 6 months of the initial procedure.

Outcomes Measured

Technical success was defined as selective catheterization and embolization from at least one feeding artery of the knee joint. All patients were clinically evaluated at 1, 4, and 6 months and every 6 months thereafter for a maximum of 4 years by using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores, total WOMAC scores, and VAS pain scores. The WOMAC is a widely used, disease-specific measure for knee OA that consists of 24 items: five regarding pain, two regarding stiffness, and 17 regarding physical function; possible score ranges for each subset of items are as follows: pain, 0–20; stiffness, 0–8; and physical function, 0–68 (13). Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitation. Clinical success was defined as improved pain symptoms (50% reduction in WOMAC pain score vs baseline) at 6 months after the first transcatheter arterial embolization procedure. Clinical failure was defined by the absence of the aforementioned criteria. During follow-up, recurrence of pain at a level exceeding 50% of the initial WOMAC pain score and persisting more than 2 months was considered clinical failure. The use of other conservative therapies was recorded at every follow-up visit.

MR imaging assessment was performed before treatment and 2 years after embolization in 29 patients (35 knees) treated between June 2012 and September 2014. Images were analyzed by using the Whole-Organ Magnetic Resonance Scoring (WORMS) system (14).

Adverse events were reported according to the Society of Interventional Radiology classification system. Patients were also asked during the follow-up period whether they had any of the following symptoms: newly occurring pain, peripheral paresthesia, knee instability, or muscle weakness. Patients were encouraged to mention any other symptoms at every visit.

Statistical Analysis

The primary endpoint (clinical success) was assessed on an intent-to-treat basis; outcomes were summarized with binomial responses and are reported with the corresponding two-sided exact 95% confidence interval (CI) per the Clopper–Pearson method. The total sample size needed to test the null hypothesis that the probability of observing clinical success was 0.6 or less versus the alternative that the probability was 0.75 or more was estimated at 85 knees (power of 0.90). Considering protocol deviations, a total sample size of 95 was planned. The proportion of clinical success over time was analyzed by Kaplan–Meier method. Baseline and outcome variables were compared by Dunnett post hoc test to determine changes in WOMAC and VAS scores before and after the procedure at every follow-up visit. WORMS scores between baseline and 2 years of follow-up were compared by Mann–Whitney *U* test. All statistical analyses were performed by using SPSS software

(version 11.0; SPSS, Chicago, Illinois). A P value of $< .05$ was considered statistically significant.

RESULTS

From June 2012 to March 2016, transcatheter arterial embolization was performed on 95 knees in 72 patients. Abnormal vessels were found to originate from a mean of 3.2 arteries per knee, including the superior patellar artery (n = 32), descending genicular artery (n = 84), lateral superior genicular artery (n = 52), median genicular artery (n = 30), medial superior genicular artery (n = 26), medial inferior genicular artery (n = 74), lateral inferior genicular artery (n = 75), and anterior tibial recurrent artery (n = 18). Embolization was technically successful in all patients. Mean amounts of embolic material used to treat one knee were 0.31 g (range, 0.1–0.6 g) for IPM/CS and 0.12 mL (range, 0.07–0.2 mL) for Embozene. During infusion of the contrast agent or embolic material in the region responsible for pain, patients reported pain, itching, or a sensation of heat at the site where they usually feel symptoms (we defined this event as "evoked pain"). This finding was useful in identifying the culprit artery during the procedure. A second transcatheter arterial embolization was required in 13 knees (KL grade 1/2, n = 8; KL grade 3, n = 5) at a median of 4 months (range, 2–5 mo) after the first embolization for insufficient decrease in pain (n = 7) or short-term recurrence of pain (n = 6). Four patients were lost to follow-up, and these cases were classified as clinical failures.

Mean WOMAC pain scores decreased significantly from 12.1 ± 2.3 at baseline to 6.2 ± 4.0 at 1 month, 4.4 ± 3.5 at 4 months, 3.7 ± 1.8 at 6 months, 3.0 ± 3.1 at 12 months, and 2.6 ± 3.4 at 24 months after the first transcatheter arterial embolization procedure (all $P < .001$). The intent-to-treat clinical success rate at 6 months of follow-up was 86.3% (95% CI, 78%–92%). The mean total WOMAC score also decreased significantly from 43 ± 8.3 at baseline to 24 ± 14, 14.8 ± 11, 11.2 ± 10, 8.2 ± 8.5, and 6.2 ± 6.4 at 1, 4, 6, 12, and 24 months, respectively (all $P < .001$). The mean VAS score significantly decreased from 72 ± 16 at baseline to 38 ± 23, 29 ± 22, 19 ± 21, 13 ± 21, and 14 ± 17 at 1, 4, 6, 12, and 24 months, respectively (all $P < .001$). There was no significant difference in clinical success at 6 months after transcatheter arterial embolization between patients treated with IPM/CS and those treated with Embozene (86.4% and 85.7%, respectively; $P = 1.000$). Patients reported a decrease in the dose of medication used and frequency of other treatments after the procedure (Table 2).

During the extended follow-up period (> 6 mo after embolization), four knees in four patients showed symptom recurrence at a level that met the criteria for clinical failure (pain recurrence of intensity greater than 50% of initial WOMAC pain score and persisting more than 2 mo). The Kaplan–Meier estimates of cumulative clinical success at 2 years after first the embolization were 85.2% (95% CI, 72%–92%) in knees with KL grade 1/2 OA and 69.8% (95% CI, 49%–84%) in knees with KL grade 3 OA (Fig 3).

Table 2. Details of Patients Who Used Other Conservative Treatments

Treatment	Before Treatment (n = 72)	1 mo (n = 72)	6 mo (n = 72)	12 mo (n = 52)	24 mo (n = 30)
Oral NSAIDs					
Daily	28	8	2	1	1
As needed	11	8	4	3	3
Oral opioids					
Daily	20	8	3	2	2
As needed	2	4	0	0	0
HA injection					
Routinely	29	0	0	0	0
As needed	14	11	5	3	2

HA = hyaluronic acid; NSAID = nonsteroidal antiinflammatory drug.

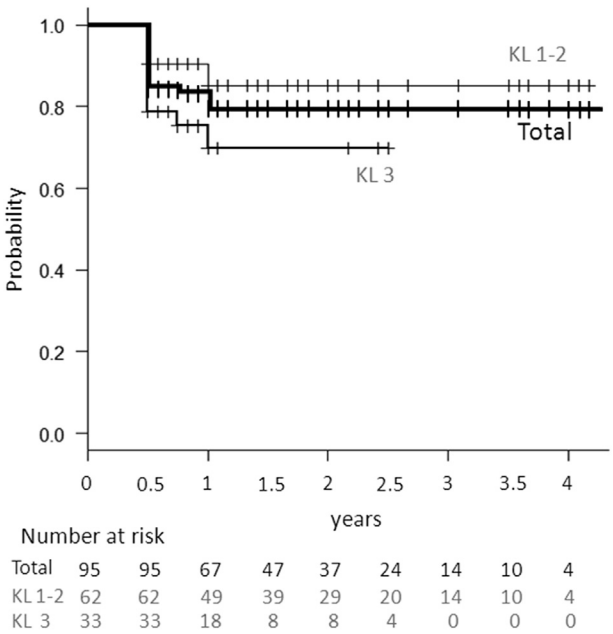

Figure 3. Kaplan–Meier estimates of cumulative clinical success after transcatheter arterial embolization.

MR Imaging Assessment

MR imaging examination of 35 knees in 29 patients was performed at 2 years after transcatheter arterial embolization; no bone marrow necrosis, aggressive cartilage loss, tendon or ligament rupture, or muscle atrophy was observed in any of the patients (Fig 4). No significant difference in WORMS scores was noted between baseline and 2 years after embolization with regard to cartilage, marrow abnormality, bone cysts, bone attrition, osteophyte, menisci, and ligaments (Table 3). WORMS scores for synovitis improved significantly ($P = .0016$) at the final follow-up compared with baseline (Table 3).

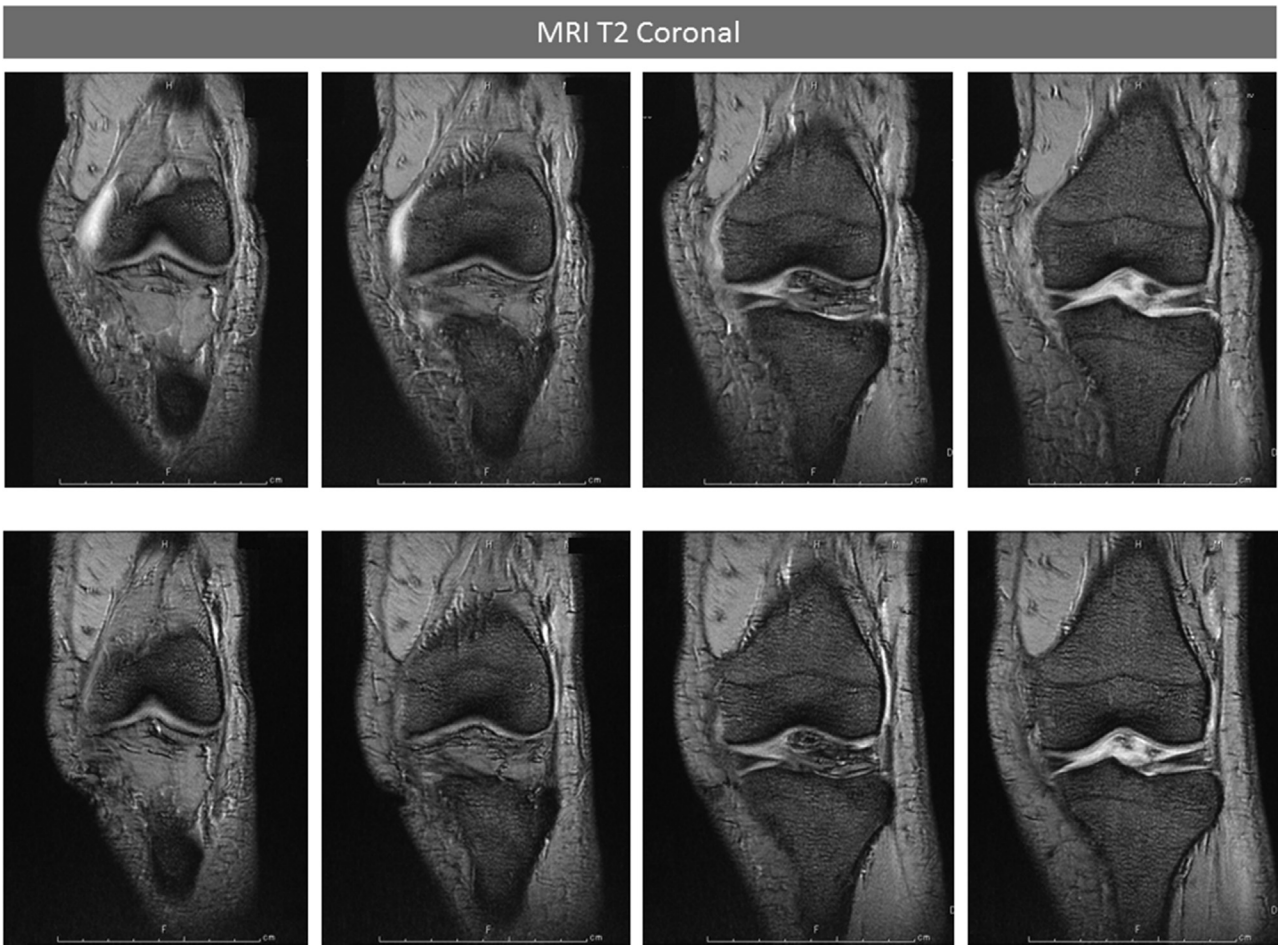

Figure 4. MR images at baseline (upper row) and 2 years after transcatheter arterial embolization (lower row). Coronal T2-weighted gradient-echo MR images show joint effusion at baseline and decreased joint effusion and no evidence of marrow necrosis or other abnormalities at 2 years after embolization.

Adverse Events

There were no major adverse events related to the procedures in either patient group (IPM/CS or Embozene). There was no incidence of tissue necrosis, dermal ulcers, or peripheral paresthesia in any embolized territory during the follow-up period. Moderate subcutaneous hemorrhage at the puncture site in 12 patients resolved within 1 week. Four of seven patients treated with Embozene showed transient cutaneous color change on the treated knee, which resolved spontaneously within 1 month.

Table 3. Change in WORMS Scores

WORMS Score	Baseline	2 y	*P* Value
Cartilage	22.4 ± 9.9	22.5 ± 9.9	.956
Marrow abnormality	1.89 ± 1.8	1.75 ± 1.9	.603
Bone cysts	0.34 ± 0.6	0.35 ± 0.6	.771
Bone attrition	1.58 ± 1.3	1.62 ± 1.4	.992
Osteophytes	12.6 ± 9.1	14.3 ± 10.2	.422
Menisci	1.62 ± 1.6	1.69 ± 1.6	.856
Ligament	0.07 ± 0.2	0.07 ± 0.2	1.000
Synovitis	1.52 ± 0.8	0.72 ± 0.6	.0016
Total	42.0 ± 20.1	43.1 ± 21.3	.838

WORMS = Whole-Organ Magnetic Resonance Imaging Scoring.

DISCUSSION

The present study demonstrates that transcatheter arterial embolization improves pain symptoms and knee function for as long as 4 years of follow-up. No serious adverse events were noted. Minor complications occurred, such as moderate subcutaneous hemorrhage at the puncture site and transient cutaneous color change on the treated knee, all of which resolved without treatment. MR imaging evaluation at 2 years after embolization showed a significant improvement in synovitis, a slight progression of osteophytes, and no osteonecrosis or other evidence of ischemic complications.

It has been previously suggested that cartilage lesions, bone marrow lesions, and meniscus damage are associated with knee OA symptoms. In contrast to this notion, a study in which 3-T MR imaging of both knees was performed in 169 patients with knee OA and unilateral chronic knee pain

(15) found a high degree of symmetric pathology between both knees for such lesions, as assessed by WORMS; this finding suggests that these lesions are more nonspecific than previously believed. On the contrary, assessment of knee OA with contrast-enhanced MR imaging has demonstrated that certain postcontrast patterns within the synovium and periarticular adipose tissue are associated with pain symptoms (16,17).

In the present study, abnormal neovessels were seen on angiography in all patients; these vessels were located mainly within the periarticular soft tissue (synovium, infrapatellar fat pad, periosteum, and joint capsule) and were often observed to be in a location consistent with the sites of tenderness, suggesting that the prevalence of vascular changes in mild to moderate radiographic knee OA is quite high and that OA pain and local tenderness could be related to abnormal neoangiogenesis. MR imaging evaluation at 2 years of follow-up showed improvement in synovitis score, which bolsters the hypothesis that abnormal neoangiogenesis is an important factor in inflammation (and therefore pain) and that transcatheter arterial embolization can reduce inflammation by occluding these abnormal vessels.

In the present study, patients who had more severe degenerative changes (ie, KL grade 3) showed a lower frequency of clinical success at 6 months after transcatheter arterial embolization than those with mild changes (ie, KL grade 1/2). A subset of patients in both groups experienced pain recurrence after initial clinical success. Knee OA is an age-related disease with no prospect for spontaneous recovery; it is therefore expected that structural changes and associated inflammation will continue to progress and that pain can recur, especially in patients with severe degenerative changes. Therefore, although embolization cannot treat knee OA completely or reverse its natural progression, it seems to be an effective additional option to alleviate pain, decrease the use of pharmacologic analgesic agents and injection therapies, and improve quality of life. Indeed, in the present case series, embolization allowed a reduction in the use of oral nonsteroidal antiinflammatory drugs and oral opioid agents and a reduction in the frequency of use of injection therapies.

The present study primarily used a nonpermanent embolic material, IPM/CS (n = 88 knees), but 75-μm Embozene spheres were used for patients who had contraindications to IPM/CS (n = 7 knees). There was no significant difference in clinical success between these two groups. Previous studies of postembolization inflammation in uterine artery embolization (18,19) have shown that embolization is a cause of inflammation in the long term (ie, foreign body reaction). In the present study, we hypothesize that the use of a small amount of Embozene (mean, 0.12 mL; range, 0.07–0.2 mL) or a nonpermanent embolic agent (eg, IPM/CS) diminishes the risk of significant tissue inflammation and symptomatic active foreign body reaction while maintaining a sufficient occluding effect to suppress small-caliber neoangiogenesis. Further studies are warranted to explore the postembolization phenomenon at the tissue level.

There may be several concerns about applying embolization to knee OA, such as the risk of ischemic events, including osteonecrosis, muscle atrophy, peripheral paresthesia, or neuropathic joint diseases such as Charcot joint. Although all patients in the present study were repeatedly asked and encouraged to report symptoms suggestive of these pathologic conditions, none reported any such symptoms. On the MR imaging evaluation at 2 years after the first transcatheter arterial embolization, no ischemic findings consistent with osteonecrosis or periarticular soft-tissue abnormalities were detected. The absence of such adverse events may be related to the embolic technique used in the present study, especially the use of small amounts of embolic material.

One potential concern with reducing pain symptoms in patients with knee OA is that reducing pain will improve their ability to walk, leading to increased joint loading and consequent progression of cartilage degeneration. However, in our MR imaging evaluation at 2 years of follow-up, the WORMS cartilage score was almost unchanged from baseline. On the contrary, improvement in synovitis score was noted. Lately, there has been increasing interest in synovitis as a predictive factor in the structural progression of knee OA, as it may contribute to the progression of cartilage loss by promoting the production of matrix proteases (20). Longitudinal studies that used arthroscopy in patients with knee OA have demonstrated a positive correlation between the presence of hypervascularization in the synovium and the degree of progression of cartilage lesions over time (21). These findings, combined with the results of our MR imaging evaluations after 2 years of follow-up, suggest that transcatheter arterial embolization might even help to delay the progression of OA changes by improving synovitis. Nevertheless, embolization outcomes should be carefully investigated in larger, longitudinal comparative studies.

Obesity is one of the main risk factors for symptomatic knee OA (22). In the present study, the proportion of patients with high body mass index (> 30 kg/m^2) was low (eight of 72; 11%), a reflection of the fact that the patients enrolled in this study were Asian, an ethnic group with a low incidence of obesity. Therefore, further investigation of the effectiveness of this treatment in other countries and other ethnic groups is certainly needed.

The limitations of the present midterm follow-up study include a small sample size and the absence of a control group; furthermore, participants were not blinded to their treatment and could continue their previous conservative therapies after transcatheter arterial embolization. Further investigation is warranted to validate the findings of the present study.

In conclusion, transcatheter arterial embolization is a potential treatment option in patients with mild to moderate radiographic knee OA that is resistant to conservative treatment.

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