NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of genicular artery embolisation for pain from knee osteoarthritis

In knee osteoarthritis, new blood vessels can grow from the blood vessel that supplies blood to the knee (the genicular artery). This contributes to inflammation and pain in the knee joint. In this procedure, a tube is inserted into an artery in the groin and passed into the genicular artery. Tiny plastic particles are then injected into the new blood vessels. This blocks them (embolisation) and reduces blood flow around the knee joint. The aim is to reduce pain and improve quality of life.

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Abbreviations

Word or phrase	Abbreviation
Bone marrow lesion	BML
Confidence interval	CI
Cardiovascular and interventional radiological society of Europe classification system	CIRSE
Genicular artery embolisation	GAE
Imipenem/cilastatin sodium	IPM/CS
Interquartile range	IQR
Kellgren and Lawrence	KL
Knee injury and osteoarthritis outcome score	KOOS
Minimal clinically important difference	MCID
Magnetic resonance imaging	MRI
Nonsteroidal anti-inflammatory drug	NSAID
Standard deviation	SD
Society of Interventional Radiology	SIR
Short tau inversion recovery	STIR
Total knee replacement	TKR
Visual analogue scale	VAS
Western Ontario and McMaster Universities Osteoarthritis Index	WOMAC
Whole-organ magnetic resonance imaging score	WORMS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in November 2020.

Procedure name

- Genicular artery embolisation for pain from knee osteoarthritis

Professional societies

- British Association for Surgery of the Knee
- British Orthopaedic Association
- British Society of Interventional Radiology
- British Society of Rheumatology
- Chartered Society of Physiotherapy

Description of the procedure

Indications and current treatment

Osteoarthritis is characterised by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. Knees are one of the most affected joints, with pain being a significant symptom. Angiogenesis is believed to contribute to inflammation, structure damage and pain. This is because the increased vascular network carries inflammatory cells to the synovium and other joint tissues and promotes additional hyperplasia and inflammation in other vessels, leading to bone and cartilage destruction. Angiogenesis also enables the growth of new unmyelinated sensory nerves, which contributes to pain.

For pain secondary to knee osteoarthritis, various treatments are available, including nonpharmacologic (such as physiotherapy), pharmacologic (such as analgesics and hyaluronic acid injections) and surgical approaches (such as knee arthroplasty). Treatment most commonly involves a combination of pharmacologic therapies and non-pharmacologic interventions. When nonpharmacologic and pharmacologic interventions do not work or symptoms are severe, surgery may be needed.

What the procedure involves

This procedure aims to relieve pain by embolising the pathological new vessels while maintaining the larger vascular supply to the bone.

Before the procedure, contrast-enhanced magnetic resonance imaging (MRI) of the knee is done to allow non-invasive assessment of synovial hypervascularity.

This procedure is usually done using local anaesthesia with or without sedation. A catheter is passed through an introducer sheath in the femoral artery and then navigated into the genicular arteries supplying the knee to perform lower extremity angiography on the targeted side. Once the abnormal new vessels arising from these arteries are identified, a microcatheter is navigated into them and, under fluoroscopic guidance, tiny embolisation particles are then delivered until the blood flow is stopped.

After the introducer sheath and catheter are removed, haemostasis is achieved with manual compression or a vascular closure device. The patient often goes home the same day. This procedure generally takes between 45 and 90 minutes.

Outcome measures

The Kellgren and Lawrence (KL) system is a common method of classifying the severity of osteoarthritis using 5 grades:

- Grade 0 (none): definite absence of X-ray changes of osteoarthritis.
- Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping.
- Grade 2 (minimal): definite osteophytes and possible joint space narrowing.
- Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
- Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a disease-specific measure for knee osteoarthritis that consists of 24 items: 5 items about pain, 2 items about stiffness and 17 items about physical function. Possible score ranges for each subset of items are as follows: pain 0 to 20, stiffness 0 to 8, and physical function 0 to 68. Higher scores on the WOMAC indicate worse pain, stiffness and functional limitation.

The Knee Injury and Osteoarthritis Outcome Score (KOOS, an extension of the WOMAC Osteoarthritis Index) is a knee-specific instrument, assessing the patients' opinion about their knee and associated problems. It holds 42 items in 5 separately scored subscales: pain, joint symptoms, function in daily living, function in sport and recreation, and knee-related quality of life. The maximum score is 100, indicating no knee problems. The minimum score is 0, indicating severe knee problems.

Efficacy summary

Pain relief

In a case series of 72 patients (95 knees), the mean WOMAC pain score statistically significantly decreased 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 genicular artery embolisation (GAE) (all $p<0.001$) (Okuno 2017). The intent-to-treat clinical success (defined as a decrease of at least 50% in WOMAC pain score compared with baseline) rate at 6-month follow up was 86% (95% confidence interval [CI] 78% to 92%). The Kaplan-Meier estimate of cumulative clinical success at 2 years after the first embolisation was 85% (95% CI 72% to 92%) in knees with KL grade 1 or 2 osteoarthritis and 70% (95% CI 49% to 84%) in knees with KL grade 3 osteoarthritis. In the same study, mean visual analogue scale (VAS, 100-mm scale) score statistically significantly decreased from 72±16 mm at baseline to 38±23 mm, 29±22 mm, 19±21 mm, 13±21 mm, and 14±17 mm at 1, 4, 6, 12 and 24 months after the procedure, respectively (all $p<0.001$).

In a case series of 20 patients (20 knees), the mean VAS score decreased from 76±14 mm (95% CI 70 to 83) at baseline to 22±19 mm (95% CI 13 to 31) at 1 month, 34±26 mm (95% CI 21 to 46) at 3 months, and 31±28 mm (95% CI 17 to 45) at 6 months after the procedure (Bagla 2020). There was a statistically significant decrease in mean VAS score between baseline and 6 months (44±30, 95% CI 29 to 59, $p<0.0001$) and a MCID (defined as a 20% reduction in VAS score compared with baseline) was reported in 85% (95% CI 62% to 97%) of patients at 6-month follow up.

In a case series of 41 patients (71 knees), the mean VAS (10-point scale) score statistically significantly decreased from 5.5±2.2 at baseline to 3.2±2.1 at 1 day, 3.1±1.9 at 1 week, 2.9±1.7 at 1 month, 2.2±1.7 at 3 months and 1.9±1.5 at 6 months after GAE (all $p<0.01$) for patients with mild-to-moderate osteoarthritis (Lee 2019). For patients with severe osteoarthritis, mean VAS scores at baseline and 1 day, 1 week, 1 month, 3 months and 6 months after the procedure were 6.3±2.2 and 4.1±2.1, 4.1±2.1, 4.4±2.01 5.4±2.0 and 5.9±2.1, respectively. The decrease in pain was statistically significant at 1 month after the procedure ($p<0.01$) but not from 3 to 6 months. In the same study, clinical success (defined as a decrease of at least 50% in VAS score compared with baseline) was achieved in 33 patients (59 knees) with mild-to-moderate osteoarthritis at 3 months after the procedure and maintained at a mean follow up of 10 months (SD 3) (Lee 2019). For patients with severe osteoarthritis, clinical success was not achieved at all follow-ups.

In a case series of 38 patients, the mean VAS score statistically significantly reduced from 60±20 mm (95% CI 53 to 66) at baseline to 32±25 mm (95% CI 24 to 42) at 6 weeks (p<0.001), 36±24 mm (95% CI 28 to 44) at 3 months (p<0.001), and 45±30 (95% CI 30 to 60) at 12 months (p<0.05) (Little 2021).

In a systematic review of 3 studies (n=133 patients with 186 treated knees), mean VAS across all studies decreased from 66.5 mm at baseline to 33.5 mm at 1 day, 32.7 mm at 1 week, 33.8 mm at 1 month, 28.9 mm at 3 months, 29.0 mm at 4 months, 22.3 mm at 6 months, 14.8 mm at 1 year and 14.0 mm at 2 years after GAE (Casadaban 2020).

Improvement in knee symptoms and function

In the case series of 72 patients, the mean total WOMAC score statistically significantly decreased 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 after the procedure, respectively (all p<0.001) (Okuno 2017).

In the case series of 20 patients, the mean total WOMAC score decreased from 61±12 (95% CI 56 to 67) at baseline to 24±17 (95% CI 16 to 32) at 1 month, 31±21 (95% CI 21 to 41) at 3 months, and 31±26 (95% CI 18 to 44) at 6 months after GAE (Bagla 2020). The decrease in mean WOMAC score between baseline and 6-month follow up was statistically significant (31±23, 95% CI 19 to 42, p<0.0001) and a minimal clinically important difference (MCID; defined as a 16% reduction in total WOMAC score compared with baseline) was reported in 80% of patients (95% CI 56% to 94%) at 6-month follow up.

In a case series of 10 patients, the proportions of ‘responders’ at 1, 6, 12 and 24 months after GAE were 70% (n=7), 70% (n=7), 60% (n=6) and 30% (n=3) respectively (Landers 2020). Of the 3 responders at 24 months, 2 had repeat embolisation after the 12-month assessment. A responder was defined as meeting at least 2 of the following criteria: (a) pain (KOOS) improved more than 20% from baseline and absolute change was more than 10 points on a 0 to 100 interval scale; (b) function in daily living scale (KOOS) improved more than 20% from baseline and absolute change was more than 10 points on a 0 to 100 interval scale; (c) patient’s global assessment of ‘moderately better’ or ‘much better’. In the same study, improvements in median 6-minute walk test scores at 1, 6, 12 and 24 months after the procedure from baseline were 26%, 23%, 26% and 12% respectively. In the same study, improvements in median 30-second chair stand test scores at 1, 6, 12 and 24 months after the procedure from baseline were 37%, 33%, 43% and 45% respectively.

In the case series of 38 patients, improvements in mean KOOS subscales from baseline to 3 months were statistically significant (daily living 52.62 compared

with 67.56; sports and recreational activities 20.16 compared with 33.28, p<0.01; pain 45.46 compared with 62.93; quality of life 21.48 compared with 41.21; and symptoms and stiffness 47.21 compared with 64.40; all p<0.01) (Little 2021). A MCID (defined as an improvement of at least 10 points in KOOS subscales compared with baseline) at 3 months was met by 69% of patients for symptoms and stiffness, 56% for pain, 53% for daily living, 59% for sports and recreation and 69% for quality of life. At 1-year follow up, statistically significant improvement was found in sports and recreational activities (20.16 at baseline compared with 27.19 at 12 months, p<0.03), pain (45.46 compared with 57.47, p=0.02), quality of life (21.48 compared with 36.97, p<0.01) and symptoms and stiffness (47.21 compared with 56.92, p<0.01) but not in daily living (52.62 compared with 59.83, p=0.06). A MCID was reported in 63% of patients for symptoms and stiffness, 56% for pain, 50% for daily living, 44% for sports and recreation, and 63% for quality of life.

In the systematic review of 3 studies, the mean total WOMAC score improved from 45.7 at baseline to 24.0, 31.0, 14.8, 14.6, 8.2 and 6.2 at 1, 3, 4, 6, 12 and 24 months after GAE, respectively (2 studies) (Casadaban 2020).

Reduction in medication and physical therapy

In the case series of 72 patients, the use of regular analgesia decreased after the procedure (baseline: daily oral nonsteroidal anti-inflammatory drugs [NSAIDs] n=28, daily opioids n=20 and routine hyaluronic acid injection n=29; 12-month and 24-month follow up: daily NSAIDs n=1, daily opioids n=2, routine hyaluronic acid injection n=0) (Okuno 2017).

In the case series of 20 patients, 65% of patients (95% CI 41% to 85%) reported a decrease in daily analgesic medication use at 6-month follow up (Bagla 2020).

In the case series of 41 patients (71 knees), the use of conventional treatments decreased between baseline and 12 months after the procedure in patients with mild-to-moderate knee osteoarthritis (NSAIDs, 46 compared with 9; hyaluronic acid injections, 39 compared with 2; physical therapy, 39 compared with 2) and in patients with severe knee osteoarthritis (NSAIDs, 10 compared with 3; hyaluronic acid injections, 10 compared with 1; physical therapy, 10 compared with 1) (Lee 2019).

In the case series of 10 patients, there was a reduction in the use of medication from baseline (paracetamol n=6, NSAIDs n=2) to 12 months (paracetamol n=4, NSAIDs n=1) and 24 months (paracetamol n=5, NSAIDs n=0) after the procedure (Landers 2020)

In the case series of 38 patients, there was a reduction in the use of regular analgesia after the procedure (32 patients who had GAE at baseline:

paracetamol=8, NSAIDs=10, opiates =4; 3 months: paracetamol=7, NSAIDs=5, opiates=3; 1 year: paracetamol=4, NSAIDs=4, opiates=3) (Little 2021).

In the systematic review of 3 studies, the use of NSAIDs decreased between baseline and 6 months after the procedure (65% [98/151] compared with 18% [27/151]; 3 studies) in patients with mild-to-moderate knee osteoarthritis (Casadaban 2020).

Repeat genicular artery embolisation

In the case series of 72 patients, a second embolisation was needed in 13 knees (KL grade 1 or 2, n=8; KL grade 3, n=5) at a median of 4 months (range 2 to 5 months) after the first embolisation for insufficient decrease in pain (n=7) or short-term recurrence of pain (n=6) (Okuno 2017).

In the case series of 10 patients, 6 patients had repeat embolisation after the 12-month assessment, and of these 6 patients, 3 were responders to treatment at 12 months (Landers 2020). Neovessels were identified in these patients at sites that corresponded to knee pain and embolisation was successfully achieved using imipenem/cilastatin sodium (IPM/CS).

Additional treatments

In the case series of 41 patients, 3 patients with severe osteoarthritis received a knee joint replacement at 6 months after the procedure (Lee 2019).

In the case series of 10 patients, 2 patients had a total knee replacement (TKR) after the procedure (Landers 2020). Of these, 1 patient reported no treatment benefit after GAE and knee pain continued to increase over the next 12 months. The patient did not choose repeat embolisation and had a TKR 17 months after the procedure. The other patient reported that knee pain was ‘much better’ at 12 months (global assessment) and elected for repeat embolisation because of ‘mild’ daily knee pain (KOOS). She reported that pain was ‘moderately better’ (global assessment) 1 month after the repeat embolisation but had a TKR 5 months later because of ongoing knee pain.

In the case series of 38 patients, 2 patients did not have adequate symptomatic improvement after GAE and subsequently had a knee replacement at a mean of 4 months after the procedure (Little 2021).

MRI assessment

In the case series of 72 patients, mean whole-organ magnetic resonance imaging score (WORMS) for synovitis statistically significantly improved from 1.52±0.8 at baseline to 0.72±0.6 at 2 years after the first embolisation (p=0.0016) (Okuno

2017). There was no statistically significant difference between baseline and 2 years after the procedure in mean WORMS for cartilage (22.4±9.9 compared with 22.5±9.9), marrow abnormality (1.89±1.8 compared with 1.75±1.9), bone cysts (0.34±0.6 compared with 0.35±0.6), bone attrition (1.58±1.3 compared with 1.62±1.4), osteophyte (12.6±9.1 compared with 14.3±10.2), menisci (1.62±1.6 compared with 1.69±1.6) and ligaments (0.07±0.2 compared with 0.07±0.2).

In the case series of 38 patients, mean WORMS statistically significantly improved in synovitis from 1.73±0.88 at baseline to 1.13±0.51 at 1-year follow up ($p=0.01$) and worsened in bone attrition (1.13±1.19 compared with 1.73±1.44, $p=0.03$) and osteophytes (19.47±12.82 compared with 24.4 compared with 15.65, $p=0.02$) (Little 2021). At the same period, no statistically significant difference was found in mean WORMS for cartilage (24±11.42 compared with 26.8±11.21), marrow (4.53±4.47 compared with 5.2±4.57), bone cysts (1±1.41 compared with 0.93±1.22), menisci (2.73±2.22 compared with 2.87±2.23) and ligaments (0.13±0.35 compared with 0.13±0.35).

Patient satisfaction

In the case series of 38 patients, a pooled analysis of the patient satisfaction questionnaire results showed that 75% of patients were positive ($p<0.05$) about GAE as a treatment for knee osteoarthritis (Little 2021).

Safety summary

Haemorrhage or haematoma at access site

Moderate subcutaneous haemorrhage at the puncture site was reported in 12 patients in the case series of 72 patients (Okuno 2017). All these events resolved within 1 week without treatment.

Small access site haematoma was reported in 1 patient in the case series of 20 patients (Bagla 2020).

Subcutaneous haematoma at the puncture site was described in 5 patients (4 with mild-to-moderate osteoarthritis and 1 with severe osteoarthritis) in the case series of 41 (71 knees) patients (Lee 2019). All events spontaneously resolved within 3 weeks.

Moderate-sized haematoma at the puncture site was reported in 1 patient in the case series of 10 patients and this resolved over 2 weeks (severity classification: mild) (Landers 2020).

Small self-limiting groin haematoma was reported in 1 patient in the case series of 38 patients (Little 2021).

Puncture-site haematoma or haemorrhage was described in 10% (18/186) of treated knees and resolved within 1 to 3 weeks in the systematic review of 3 studies (Casadaban 2020).

Paraesthesia

Great toe plantar numbness was reported in 2 patients in the case series of 20 patients (Bagla 2020). These 2 patients had gabapentin for 2 weeks.

Skin discoloration

Transient cutaneous colour change on the treated knee was described in 4 patients who had embolisation using Embozene in the case series of 72 patients (Okuno 2017). These events resolved spontaneously within 1 month.

Skin discoloration without ulcer was reported in 13 patients in the case series of 20 patients (Bagla 2020). These events resolved within 3 months without intervention.

Skin redness in the embolised area was described in 4 patients (3 with mild-to-moderate osteoarthritis and 1 with severe osteoarthritis) in the case series of 41 (71 knees) patients and this disappeared within 3 weeks (Lee 2019).

Mild self-limiting skin discoloration over the embolised area was reported in 4 patients in the case series of 38 patients (Little 2021). This was caused by non-target cutaneous embolisation and completely resolved within 3 weeks.

Skin change including transient erythema in the region of embolisation without ulceration was reported in 11% (21/186) of treated knees in the systematic review of 3 studies (Casadaban 2020). All these events resolved without treatment. For different embolic materials, skin change was described in 63% (17/27) of knees that were embolised using Embozene and lasted 1 to 3 months, and in 2.5% (4/159) of knees that were embolised using IPM/CS and lasted about 3 weeks.

Fever

Mild fever was reported in 1 patient with mild-to-moderate osteoarthritis in the case series of 41 (71 knees) patients (Lee 2019). This subsided within 1 day.

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, a professional expert listed the following anecdotal and theoretical adverse events: skin discolouration over the embolised territory and deep vein thrombosis.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to genicular artery embolisation for pain from knee osteoarthritis. The following databases were searched, covering the period from their start to 24 November 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with knee pain secondary to osteoarthritis.
Intervention/test	Genicular artery embolisation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 181 patients from 1 systematic review and 5 case series (Okuno 2017; Bagla 2020; Lee 2019; Landers 2020; Little 2021; Casadaban 2020).

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on genicular artery embolisation for pain from knee osteoarthritis

Study 1 Okuno Y (2017)

Study details

Study type	**Case series**
Country	Japan (single centre)
Recruitment period	2012 to 2016
Study population and number	n=72 (95 knees) Patients with moderate to severe knee pain secondary to osteoarthritis
Age and sex	Mean 64.4 years; 68% (49/72) female BMI: Mean 25.1 kilograms per square metre
Patient selection criteria	Inclusion criteria: presence of knee pain, KL grade 1 to 3 assessed by routine weight-bearing knee radiographs, local tenderness around the knee, patient age 40 to 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 (VAS score >50 mm). Exclusion criteria: osteonecrosis confirmed by MRI, local infection, malignancy, advanced atherosclerosis, rheumatoid arthritis and previous knee surgery.
Technique	Under local anaesthesia, ipsilateral antegrade femoral artery access was done using a 3-French sheath. After intravenous administration of 2,000 IU heparin, a 3-French angiographic catheter (Judkins Right 2.5; Medikit) was used. After the abnormal vessels were identified, embolic material was infused - 65 patients (88 knees) were embolised with IPM/CS (Primaxin; Merck, Whitehouse Station, New Jersey) and 7 patients (7 knees) with 75-μm Embozene. The embolisation endpoint was suppression or reduction in the filling of (and therefore blood flow in) abnormal vessels visible on angiography. Haemostasis 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 could continue previous conservative therapies. A second embolisation procedure was considered if pain persisted or relapsed within 6 months of the initial procedure.
Follow-up	4 years
Conflict of interest/source of funding	YO received personal fees from Terumo (Tokyo, Japan) and Asahi Intec (Nagoya, Japan). None of the other authors identified a conflict of interest.

Analysis

IP overview: Genicular artery embolisation for pain from knee osteoarthritis

Follow-up issues: All patients were clinically evaluated at 1, 4, and 6 months and every 6 months thereafter for a maximum of 4 years. Four patients were lost to follow up and these were classified as clinical failures.

Study design issues: This prospective, single-centre, single-arm study evaluated the midterm clinical outcomes of transcatheter arterial embolisation in patients with mild to moderate radiographic knee osteoarthritis that is resistant to conservative management. The primary endpoint (clinical success) was assessed on an intent-to-treat basis. 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.

Technical success was defined as selective catheterisation and embolisation from at least 1 feeding artery of the knee joint. Clinical success was defined as improved pain symptoms (50% reduction in WOMAC pain score compared with baseline) at 6 months after the first embolisation procedure. Clinical failure was defined as pain recurrence of intensity greater than 50% of initial WOMAC pain score and persisting more than 2 months. 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. Adverse events were reported according to the Society of Interventional Radiology classification system.

Study population issues: Abnormal vessels were found to originate for 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). Mean pain duration was 29.7 months.

Key efficacy findings

Number of patients analysed: 72 (95 knees)

Technical success of embolisation: n=72

Clinical success after embolisation:

- Intent-to-treat at 6 months: 86.3% (95% CI 78% to 92%)
- At 6 months: IPM/CS, 86.4% compared with Embozene, 85.7%, p=1.000
- The Kaplan–Meier estimates of cumulative clinical success at 2 years: 85.2% (95% CI 72% to 92%) in knees with KL grade 1 or 2 osteoarthritis and 69.8% (95% CI 49% to 84%) in knees with KL grade 3 osteoarthritis

Clinical failure (>6 months after embolisation): n=4 (4 knees)

Second embolisation: n=13 knees (KL grade 1 or 2, n=8; KL grade 3, n=5)
This was needed at a median of 4 months (range 2 to 5 months) after the first embolisation for insufficient decrease in pain (n=7) or short-term recurrence of pain (n=6).

Details of patients who used other conservative treatments

Treatment	Before embolisation (n=72)	1 month (n=72)	6 months (n=72)	12 months (n=52)	24 months (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
Hyaluronic acid injection					
Routinely	29	0	0	0	0
As needed	14	11	5	3	2

Change in WORMS scores

WORMS score	Baseline	2 years	P value
Cartilage	22.4±9.9	22.5±9.9	0.956
Marrow abnormality	1.89±1.8	1.75±1.9	0.603
Bone cysts	0.34±0.6	0.35±0.6	0.771
Bone attrition	1.58±1.3	1.62±1.4	0.992
Osteophytes	12.6±9.1	14.3±10.2	0.422
Menisci	1.62±1.6	1.69±1.6	0.856
Ligament	0.07±0.2	0.07±0.2	1.000
Synovitis	1.52±0.8	0.72±0.6	0.0016
Total	42.0±20.1	43.1±21.3	0.838

MR imaging examination of 35 knees in 29 patients at 2 years after embolisation: no bone marrow necrosis, aggressive cartilage loss, tendon or ligament rupture, or muscle atrophy.

Change in WOMAC scores

	Baseline	1 month	4 months	6 months	12 months	24 months	P value
Mean WOMAC pain scores	12.1±2.3	6.2±4.0	4.4±3.5	3.7±1.8	3.0±3.1	2.6±3.4	<0.001
Mean total WOMAC score	43±8.3	24±14	14.8±11	11.2±10	8.2±8.5	6.2±6.4	<0.001

Mean VAS score	72±16	38±23	29±22	19±21	13±21	14±17	<0.001

Key safety findings

No major adverse events related to the procedures in the IPM/CS or Embozene group.

No incidence of tissue necrosis, dermal ulcers or peripheral paraesthesia in any embolised territory during the follow-up period.

Moderate subcutaneous haemorrhage at puncture site: n=12, this resolved within 1 week without treatment.

Transient cutaneous colour change on the treated knee: n=4 patients who had embolisation using Embozene, this resolved spontaneously within 1 month.

Study 2 Bagla S (2020)

Study details

Study type	**Case series**
Country	US (2 centres)
Recruitment period	2017 to 2018
Study population and number	n=20 (20 knees) Patients with moderate-to-severe knee pain secondary to osteoarthritis
Age and sex	Mean 59.4 years (range 49 to 84 years); 55% (11/20) female BMI: Mean 35 kilograms per square metre
Patient selection criteria	Inclusion criteria: age 40 years or older; mild-to-moderate knee osteoarthritis as determined by radiographs demonstrating KL grade 1 to 3 findings; self-reported pain of at least 5/10; and failure of conservative therapy, such as pain medication or intraarticular injections, for at least 3 months. Exclusion criteria: a history of rheumatoid arthritis, renal insufficiency, irreversible coagulopathy, previous arthroplasty, joint infection, or KL grade 4 radiographic findings.
Technique	The procedure was done using moderate sedation with midazolam and fentanyl and local anaesthesia at the arterial puncture site. Contralateral femoral artery access was done using a 6-Fr sheath. A 2.4-Fr microcatheter (j-shape angled Direxion; Boston Scientific, Natick, Massachusetts) was used to catheterise the genicular arteries, and angiography was performed to identify a 'tumour blush' pattern of opacity. Embolisation was done using either 75- (for the first 9 patients) or 100-μm (for the subsequent 11 patients) spherical particles (Embozene; Boston Scientific) to inject 0.2 ml aliquots of embolic solution until the 'tumour blush' was no longer evident. Patients were discharged on the same day.
Follow-up	6 months
Conflict of interest/source of funding	SB was a paid consultant for Boston Scientific (Marlborough, Massachusetts), Medtronic (Dublin, Ireland), Terumo (Shibuya, Tokyo, Japan), and Merit Medical (Jordan, Utah). AI was a paid consultant for Boston Scientific, BTG (London, United Kingdom), Terumo, Cook Medical (Bloomington, Indiana), EmbolX (Sunnyvale, California), ABK Biomedical (Halifax, Nova Scotia), and Crann Med (Galway, Ireland), and received research funding from Medtronic and BTG. None of the other authors identified a conflict of interest.

Analysis

Follow-up issues: Patients were assessed at 1 day, 1 month, 3 months and 6 months after the procedure. One patient was lost to follow-up for the 1- and 3-month intervals but presented for 6-month follow-up.

Study design issues: This prospective trial (NCT02850068) evaluated the safety and clinical outcomes of GAE using a permanent embolic agent. Procedures were done by interventional radiologists with 8, 5 and 5 years of

experience performing embolisation procedures. All follow-up evaluation was done by research personnel and not the operators themselves, to avoid bias. If adverse events were reported, evaluation was then done by the operators to determine severity and if treatment was warranted.

Technical success was defined as selective catheterisation and embolisation of at least 1 genicular artery. Based on MCID, 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. The study was powered to detect an MCID in WOMAC total score of 16% and VAS of 20% at 6 months. Using the baseline WOMAC total score (48.5±9.4), 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 0.5. To prevent inadequate power after a potential lost-to-follow–up rate of 30%, 20 total patients were enrolled.

Study population issues: On the basis of BMI, 2 patients were considered obese (30 to 34 kilograms per square metre) and 10 were considered morbidly obese (35 kilograms per square metre and higher). Radiographs revealed moderate osteoarthritis in 18 patients (Kellgren–Lawrence grade 2 or 3) and mild changes in 2 patients (Kellgren–Lawrence grade 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.

Key efficacy findings

Number of patients analysed: 20

Mean arteries embolised per patient: 2.5±0.9

Mean procedure time: 81±31 minutes

Mean fluoroscopy time: 29±12 minutes

Mean administered reference air kerma: 128±106 mGy

Pain medication at baseline compared with 6-month follow up

	Baseline	6-month follow up
Opiates	6	1
Acetaminophen	4	2
NSAID	13	6

Sixty-five percent of patients (95% CI 41% to 85%) reported a decrease in daily analgesic medication use.

Baseline characteristics and clinical outcomes

	Baseline		1 month		3 months		6 months	
	mean±SD	95% CI	mean±SD	95% CI	mean±SD	95% CI	mean±SD	95% CI
VAS, mm	76±14	70 to 83	22±19	13 to 31	34±26	21 to 46	31±28	17 to 45
WOMAC score	61±12	56 to 67	24±17	16 to 32	31±21	21 to 41	31±26	18 to 44

The mean decrease between baseline and 6 months was 44 for VAS (SD=30; 95% CI 29 to 59) and 31 for WOMAC (SD=23; 95% CI 19 to 42). Both decreases were statistically significant (p<0.0001).

At 1 month, all patients met the primary endpoint of an MCID in WOMAC score, and 95% (95% CI 75% to 100%) noted an MCID in VAS score.

At 6 months, 80% (95% CI, 56% to 94%) noted an MCID in WOMAC and 85% (95% CI, 62% to 97%) noted an MCID in VAS.

MRI assessment: 2 patients had small regions (<2 cm) of increased STIR signal within the marrow of their femurs on 1-month follow-up MRI. These were interpreted as nonspecific foci of inflammation without the typical imaging characteristics of infection or infarction. No further imaging was done for these 2 patients because they did not report symptoms associated with these imaging findings.

Key safety findings

Skin discoloration without ulcer: 65% (n=13). This resolved by the 3-month follow-up evaluation without intervention. 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.

Small access site haematoma: 5% (n=1)

Great toe plantar numbness: 10% (n=2). This was treated with gabapentin for 2 weeks. Plantar paraesthesia was thought to be caused by nontarget embolisation of the medial plantar nerve, a branch of the tibial nerve that receives its vascular supply from branches of the popliteal artery. 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.

All adverse events were classified as class A except for the great toe numbness, which was classified as a class B complication.

Study 3 Lee SH (2019)

Study details

Study type	**Case series (retrospective)**
Country	Korea (single centre)
Recruitment period	2017 to 2018
Study population and number	n=41 (71 knees: mild-to-moderate osteoarthritis, n=33 [59 knees] and severe osteoarthritis, n=8 [12 knees]) Patients with mild-to-severe knee pain secondary to osteoarthritis
Age and sex	Based on all 71 cases: mean 67.2 years; 76% (54/71) female BMI: mean 24.9 kilograms per square metre
Patient selection criteria	Inclusion criteria: knee osteoarthritis patients who were refractory to conservative treatments, including physical therapy, muscle strengthening, nonsteroidal anti-inflammatory drugs, and intraarticular hyaluronic acid injection therapy, and who had experienced mild-to-severe pain (10-point VAS score ≥2) for more than 3 months.
Technique	Under local anaesthesia, femoral artery access was achieved in an ultrasound-guided ipsilateral antegrade fashion followed by the insertion of a 5-Fr sheath (Terumo, Tokyo, Japan). After intravenous administration of 2,000 IU heparin, a 4-French angiographic catheter (Judkins right catheter; Merit Medical, UT, USA) was then introduced towards the distal superficial femoral artery. A suspension of 0.5 g IPM/CS (Prepenem) in 7 mL of iodinated contrast medium was used as an embolic agent. After confirming that the abnormal staining was consistent with the pain site, an IPM/CS suspension was prepared by pumping a syringe 20 times. The suspension was then injected in 0.2 mL increments until the blood flow was stagnated. Haemostasis was achieved using a vascular closure device (FemoSeal; Terumo, Tokyo, Japan) in addition to 2 hours of patient bed rest after removal of the femoral sheath. The patients were then discharged on the same day.
Follow-up	12 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were assessed at day 1, week 1 and months 1, 3, 6 and 12 after the procedure.

Study design issues: This retrospective study compared the clinical outcomes of transcatheter arterial embolisation for chronic knee pain between patients with mild-to-moderate and patients with severe knee osteoarthritis. All enrolled cases (n=71) were categorised into the 2 groups according to the KL grade: mild-to-moderate osteoarthritis (n=59, KL grade 1 to 3) and severe osteoarthritis (n=12, KL grade 4) groups.

The clinical success of the procedure was defined as a decrease of at least 50% in the VAS score compared with baseline. Adverse events were based on the Cardiovascular and Interventional Radiological Society of

Europe (CIRSE) Classification System. Minor adverse events were defined as CIRSE grade 1 to 2 and major adverse events as CIRSE grade 3 to 5.

Study population issues: A total of 71 knees in 41 patients included 30 bilateral cases. Mean pain duration was 73.2±72.2 months. At baseline, there was no statistically significant difference in age, BMI, KL grade and VAS score between the 2 groups.

Key efficacy findings

Number of patients analysed: 41 (71 knees)

Embolisation was successfully performed in all patients.

Clinical success:

- Mild-to-moderate osteoarthritis group (59 knees in 33 patients): clinical success was achieved at 3 months after the embolisation and maintained at a mean follow-up of 10 months (SD=3).
- Severe osteoarthritis group (12 knees in 8 patients): clinical success was not achieved.

Joint replacement: n=3 patients with severe osteoarthritis received joint replacement surgery at 6-month follow up.

Changes in VAS scores and conservative treatments

Group	Baseline	1 day	1 week	1 month	3 months	6 months	12 months
Mild-to-moderate osteoarthritis group (number of follow-up cases [knees])	n=59	n=59	n=59	n=59	n=59	n=59	n=19
VAS, mean±SD	5.5±2.2	3.2±2.1	3.1±1.9	2.9±1.7	2.2±1.7	1.9±1.5	1.8±2.1
Patients receiving NSAIDs	46	18	15	16	16	15	9
Patients receiving intra-articular hyaluronic acid injection	39	0	0	2	1	1	2
Patients receiving physical therapy	39	1	3	3	3	4	2
Severe osteoarthritis group (number of follow-up cases [knees])	n=12	n=12	n=12	n=12	n=12	n=9	n=3
VAS, mean±SD	6.3±2.2	4.1±2.1	4.1±2.1	4.4±2.1	5.4±2.0	5.9±2.1	5.3±1.1
Patients receiving NSAIDs	10	2	4	4	6	5	3
Patients receiving intra-articular hyaluronic acid injection	10	0	0	2	2	0	1
Patients receiving physical therapy	10	0	0	1	1	0	1

In the mild-to-moderate osteoarthritis group, the reduction in pain from the baseline to 6 months after the embolisation was statistically significant (all p=0.00).

In the severe osteoarthritis group, the reduction in pain was statistically significant between the baseline and 1-month post-embolisation ($p<0.01$).

Angiographic findings: Abnormal hypervascular staining was identified in all patients around the periarticular tissues of the knee joint, such as the synovium, fat pad, periosteum, and joint capsule. Abnormal hypervascular staining around the subchondral bone and osteochondral junction was not observed in the mild-to-moderate osteoarthritis group but equivocally identified in the severe osteoarthritis group.

Key safety findings

Subcutaneous haematomas at the puncture sites: n=5 patients (mild-to-moderate osteoarthritis, n=4; severe osteoarthritis, n=1), all events spontaneously resolved within 3 weeks.

Skin redness in the embolised areas: n=4 patients (mild-to-moderate osteoarthritis, n=3; severe osteoarthritis, n=1). This disappeared within 3 weeks.

Mild fever: n=1 patient with mild-to-moderate osteoarthritis. This subsided within 1 day.

No major adverse events because of the procedure were recorded.

Study 4 Landers S (2020)

Study details

Study type	**Case series**
Country	Australia (single centre)
Recruitment period	Not reported
Study population and number	n=10 Patients with moderate-to-severe knee pain secondary to osteoarthritis
Age and sex	Mean 62.2 years; 40% (4/10) female BMI: median 31.0 kilograms per square metre
Patient selection criteria	Inclusion criteria: patients had KL grade 1 to 2 knee osteoarthritis on x-ray (including Rosenberg projection weight-bearing radiograph), had at least moderate knee pain for ≥6 months and had failed conservative treatment. Exclusion criteria: patients had local infection, rheumatoid arthritis or seronegative arthropathies, knee arthroscopic surgery in the preceding 6 months or intra-articular injection in the preceding 6 months.
Technique	Under local anaesthetic and moderate sedation, using an antegrade transfemoral approach, a 3-F introducer sheath (Cook Medical, Bloomington, Indiana) was advanced under ultrasound guidance into the femoral artery, through which a 2.6-F microcatheter (Cook Medical) was advanced to the origin of each genicular artery and contrast medium was injected to identify the abnormal vessels. Embolisation of neovessels was achieved by manually injecting the embolic agent (1 mL solution of 90 to 180 µm polyvinyl embolic material in 5 patients and 0.5 g IPM/CS in 5 patients) in 0.2 mL increments until blood flow stagnated on angiogram. Patients were monitored for 4 hours after the procedure and then discharged home. They did not receive analgesia following the procedure. The potential for repeat GAE was discussed with patients at 12 months. Patients with no major adverse events following the initial procedure, ongoing knee pain that may or may not have responded to the initial treatment, and a desire for another procedure were eligible for repeat GAE.
Follow-up	24 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were assessed at 4 hours and then 1, 6 and 12 months after the procedure. After the 12-month assessment, 2 patients withdrew from the study and elected to have a total knee replacement.

Study design issues: This single-arm prospective pilot study (ACTRN12616000770460) determined the safety and feasibility of GAE in people with mild knee osteoarthritis and investigated the effects of GAE on pain, function and quality of life. The primary outcome was the proportion of responders at 12 months according to a modified version of the Outcome Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International responder criteria. A responder required at least 2 of the following 3 criteria: (a) pain improved >20% from baseline and absolute change >10 points on a 0 to 100 interval scale; (b) function improved >20% from baseline and absolute change >10 points on a 0 to 100 interval scale; (c) patient's global assessment of 'moderately better' or 'much better'. Pain and function were assessed with the Knee Injury and Osteoarthritis Outcome Score, using the Pain scale and Function in Daily Living scale, respectively. Secondary outcomes were responders at 1, 6, 24 months, number and type of adverse events, technical success (defined as the identification of neovessels on angiogram and cessation of contrast media filling neovessels on angiogram obtained after embolisation), pain, self-reported function, physical performance, joint symptoms, quality of life, and global knee change (7-point ordinal scale).

Procedures were conducted by a single interventional radiologist who had 3 years of experience performing embolisation of blood vessels for uncontrolled bleeding but no experience performing embolisation for musculoskeletal pain. Knee MR imaging was performed at baseline, 12 months and 24 months. MR imaging at follow-up was principally done to assess for osteonecrosis. MR imaging scans were assessed by a musculoskeletal radiologist with 15 years of experience who was independent of this study. A research assistant, trained by the study investigators, collected study data according to a standardised protocol.

Study population issues: previous treatments included analgesia/anti-inflammatory medication (n=8), physiotherapy/hydrotherapy (n=6) and intra-articular injection (n=1).

Key efficacy findings

Number of patients analysed: 10

Successful embolisation: n=10

Knee pain scores (n=10), median (range):

- Before the procedure: 5 (range 3 to 10)
- About 4 hours after the initial GAE: 0 (range 0 to 4)

Repeat GAE at 12 months: n=6 (neovessels were identified and corresponded to knee pain. Embolisation of neovessels was successfully achieved using IPM/CS.)

Knee pain scores (n=6), median (range):

- Before the procedure: 3 (range 3 to 8)
- After the repeat GAE: 1 (range 0 to 2).

Responders after GAE

	1 month	6 months	12 months	24 months
Responders	70% (n=7)	70% (n=7)	60% (n=6)	30% (n=3)

Of the 6 responders at 12 months, 2 patients used polyvinyl embolic material and 4 patients used IPM/CS.

Of the 3 responders at 24 months, 2 patients had repeat embolisation after the 12-month assessment.

Self-reported and performance-based measures

	Baseline (n=10)	1 month (n=10)	6 months (n=10)	12 months (n=10)	24 months (n=8)
KOOS pain					
Median (IQR)	54.2 (34.7 to 63.2)	70.8 (61.8 to 88.2)	66.7 (52.8 to 87.5)	62.5 (51.4 to 75.0)	51.4 (47.9 to 67.4)
% change		30.8%	23.1%	15.4%	-5.1%
KOOS symptoms					
Median (IQR)	60.7 (58.0 to 63.4)	75.0 (60.7 to 95.5)	64.3 (53.6 to 90.2)	62.5 (48.2 to 81.3)	67.9 (50.0 to 76.8)
% change		23.5%	5.9%	2.9%	11.8%
KOOS function					
Median (IQR)	65.4 (46.0 to 67.6)	80.9 (72.8 to 98.9)	83.1 (61.8 to 94.9)	79.4 (47.8 to 92.3)	60.3 (40.8 to 78.7)
% change		23.6%	27.0%	21.3%	-7.9%
KOOS sport and recreation					
Median (IQR)	37.5 (26.3 to 61.3)	70.0 (56.3 to 90.0)	80.0 (31.3 to 98.8)	45.0 (21.3 to 77.5)	27.5 (23.8 to 57.5)
% change		86.7%	113.3%	20.0%	-26.7%
KOOS quality of life					
Median (IQR)	25.0 (20.3 to 50.0)	59.4 (26.6 to 68.8)	53.1 (39.1 to 79.7)	50.0 (39.1 to 56.3)	46.9 (35.9 to 56.3)
% change		137.5%	112.5%	100.0%	87.5%
30-second chair stand test, stands					
Median (IQR)	8.3 (6.7 to 10.8)	11.3 (10.2 to 12.3)	11.0 (10.1 to 13.2)	11.8 (8.6 to 12.6)	12.0 (8.0 to 15.1)
% change		37%	33%	43%	45%
6-minute walk test, m					
Median (IQR)	343 (227 to 454)	432 (379 to 535)	421 (406 to 502)	432 (373 to 463)	385 (365 to 417)
% change		26%	23%	26%	12%
Global knee change					

Improved	60% (n=6)	70% (n=7)	70% (n=7)	70% (n=7)	50% (n=4)
No change	20% (n=2)	10% (n=1)	10% (n=1)	10% (n=1)	25% (n=2)
Worse	20% (n=2)	20% (n=2)	20% (n=2)	20% (n=2)	25% (n=2)

Change in analgesia use

	Before GAE	12 months	24 months
No. of patients taking paracetamol	6	4	5
No. of patients taking NSAIDs	2	1	0

No patients were taking opioids before and after the procedure.

Additional treatments:

- Physiotherapy: Before the 6-month assessment, 1 patient had 2 sessions of physiotherapy and had begun a home exercise program.
- Total knee replacement: n=2 after the 12-month assessment

  Of these 2 patients, 1 patient reported no treatment benefit and that his knee pain continued to increase in the 12 months following the intervention; he did not choose repeat GAE and had TKR 17 months following the procedure. The other patient reported her knee pain was 'much better' at 12 months (global assessment) and elected for repeat GAE owing to 'mild' daily knee pain (Knee Injury and Osteoarthritis Outcome Score Pain scale). She reported her pain was 'moderately better' (global assessment) 1 month after repeat GAE, but she had TKR 5 months later because of ongoing knee pain.

Key safety findings

No major adverse events were reported, and no osteonecrosis was found on knee MRI at 12 or 24 months.

Moderate-sized haematoma at the puncture site: n=1 (this resolved over 2 weeks [severity classification: mild]).

Study 5 Little M (2021)

Study details

Study type	**Case series (interim analysis)**
Country	UK (single centre)
Recruitment period	2018 to 2020
Study population and number	n=38 Patients with knee pain secondary to osteoarthritis
Age and sex	Mean 60 years; 53% (20/38) female BMI: median 30 kilograms per square metre
Patient selection criteria	Inclusion criteria: age 45 years or older, mild to moderate knee osteoarthritis as determined on X-ray as KL grade 1 to 3, and knee pain present for at least 6 months, resistant to conservative treatment (physiotherapy/analgesia/exercise/weight loss/intra-articular injections). Exclusion criteria: rheumatoid or infectious arthritis, severe knee osteoarthritis (KL grade 4), renal impairment (eGFR\45), a bleeding diathesis, irreversible coagulopathy, or previous knee arthroplasty.
Technique	Ultrasound-guided anterograde access of the common femoral artery was done, with insertion of a 4F vascular sheath (Cordis Medical, USA). After angiography was performed, a Fathom 14 guidewire (Boston Scientific, USA) was used for vessel selection, a straight-tip microcatheter (2.9 to 2.0F Pursue, Merit Medical, USA) was introduced through the base catheter into the genicular arteries supplying the pathological synovium. Glycerol trinitrite was injected through the microcatheter to optimise anterograde flow into the hypervascular synovium. A sports ice pack was placed on the skin surface of the knee corresponding to the area to be embolised. Cone-beam-CT (Philips Allura FD20) was done, injecting 6 ml of 100% iodinated contrast (Iomeron, Bracco, Italy) at 0.3 ml/s with a 6 s delay. Once a safe and effective microcatheter position was confirmed, the target vessels were embolised with 100 to 300 µm Embosphere particles (Merit Medical, USA) dilute in 20 ml (300 mg/ml) iodinated contrast (Iomeron, Bracco, Italy). Embolisation was done cautiously injecting 0.1 to 0.3 ml of embolic at a time using a 3-ml syringe. Patients recovered for 4 hours and were discharged home the same day.
Follow-up	Mean 8 months (range 3 to 12 months)
Conflict of interest/source of funding	MWL was a paid consultant for Crannmed, Boston Scientific, Guerbet, and Merit Medical. None of the other authors declared a potential conflict of interest. The study was funded by Merit medical.

Analysis

Follow-up issues: Patients were assessed at 6 weeks, 3 months (n=32) and 1 year (n=16) after the procedure.

Study design issues: This prospective single-centre pilot study (GENESIS; IRAS: 237676, CPMS: 37741) investigated the safety and feasibility of performing GAE in patients with mild to moderate knee osteoarthritis using permanent microspheres. Patients' symptoms were evaluated using KOOS and VAS, and their knee-specific analgesia used was recorded at baseline, 6 weeks, 3 months and 1 year after the procedure. Patient satisfaction questionnaires were designed to ascertain patient-reported outcome measures on the GAE procedure. Technical success was defined as selective catheterisation and embolisation of the target genicular arteries. A MCID of 10 was used for KOOS scores.

MRI of the knee was repeated at 12-month follow-up. WORMS was used to standardise imaging assessment pre and post intervention. Images were independently reviewed by two musculoskeletal radiologists with 11 and 6 years of experience. Both radiologists had prior training and experience of WORMS. They were blind to patient characteristics and outcome measures. All GAE procedures were carried out by 2 consultant interventional radiologists with 6 and 25 years' experience. Data collection was completed by the radiology research nursing team who were blind to the procedure.

All adverse events were recorded prospectively in line with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Quality Assurance Document and Standards for Classification of Complications.

Study population issues: Of the 38 patients, 18 patients with KL grade 3, 17 with KL grade 2, and 3 with KL grade 1. In terms of previous knee-specific treatments, 21 had physiotherapy, 26 had intra-articular injections, 15 had arthroscopy, 2 had acupuncture and 1 had platelet-rich plasma. At baseline, 30 patients were taking regular analgesia for their knee pain (paracetamol=12, NSAIDS=13, opiates=5). For the 32 patients having GAE, 22 took regular analgesia (paracetamol=8, NSAIDS=10, opiates=4).

Key efficacy findings

Number of patients analysed: 38

Technical success: 84%

Number of patients who were not embolised: n=6 (1 was because of significant cutaneous supply, and 3 because of anastomotic communication between the selected target genicular artery and the popliteal artery, which might have resulted in distal non-target embolisation. Two further patients were not embolised because of a lack of hyperaemic target).

Mean number of genicular arteries embolised per patient: 1.3±0.5

Mean fluoroscopy duration: 14.29±9.58 minutes

Mean cumulative air kerma: 96±75 mGy

Mean VAS at baseline was 60±20 mm (95% CI 53 to 66), reducing to 32±25 mm (95% CI 24 to 42) at 6 weeks ($p<0.001$), 36±24 mm (95% CI 28 to 44) at 3 months ($p<0.001$), and 45±30 (95% CI 30 to 60) at 12 months ($p<0.05$).

Pain: 71% (27/38) of patients reported pain on injecting contrast and embolic into the target genicular arteries. Immediately post-embolisation, these patients reported a significant improvement in this nociceptive response on repeat injection of contrast.

Knee replacement: n=2 (they did not have adequate symptomatic improvement at follow-up and subsequently underwent knee replacement surgery at a mean of 4 months following GAE.)

Use of analgesia: At 3-month follow-up, 15 patients were taking analgesia (paracetamol=7, NSAIDS=5, opioids=3). For patients completing 1-year follow-up, 11 patients were taking regular analgesia (paracetamol=4, NSAIDS=4, Opioids=3).

Mean KOOS subscales

Assessment	Visit	Mean score	P value
Daily living	Baseline	52.62	
	6 weeks	70.59	<0.01
	3 months	67.56	<0.01
	12 months	59.83	0.06
Sports and recreational activities	Baseline	20.16	
	6 weeks	39.84	<0.01
	3 months	33.28	<0.01
	12 months	27.19	0.03
Pain	Baseline	45.46	
	6 weeks	66.40	<0.01
	3 months	62.93	<0.01
	12 months	57.47	0.02
Quality of life	Baseline	21.48	
	6 weeks	46.98	<0.01
	3 months	41.21	<0.01
	12 months	36.97	<0.01
Symptoms and stiffness	Baseline	47.21	
	6 weeks	66.36	<0.01
	3 months	64.40	<0.01
	12 months	56.92	<0.01

WORMS analysis

	Baseline (mean)	Baseline (SD)	1-year mean	1-year SD	P value
Cartilage	24	11.42	26.8	11.21	0.07
Marrow	4.53	4.47	5.2	4.57	0.10
Bone cysts	1	1.41	0.93	1.22	0.75
Bone attrition	1.13	1.19	1.73	1.44	0.03
Osteophytes	19.47	12.82	24.4	15.65	0.02
Menisci	2.73	2.22	2.87	2.23	0.33
Ligaments	0.13	0.35	0.13	0.35	1
Synovitis	1.73	0.88	1.13	0.51	0.01
Total	54.73	27.48	63.2	30.51	0.008

MCID for KOOS subscale at follow up

KOOS outcome	6 weeks % of patients reaching MCID	3 months % of patients reaching MCID	1 year % of patients reaching MCID
Symptoms and stiffness	65	69	63
Pain	58	56	56
Daily living	65	53	50
Sports and recreational	61	59	44
Quality of life	81	69	63

Patient satisfaction questionnaire outcomes on acceptability of GAE

Question	Response scale	Mean response (SD)
Did you feel anxious before the procedure?	1 (no) to 10 (very)	2(3)

Did you feel anxious during the procedure?	1 (no) to 10 (very)	3 (3)
Did you feel any pain during the procedure?	1 (no) to 10 (very)	4 (3)
Was the position of lying on your back uncomfortable?	1 (no) to 10 (very)	3 (3)
Was the length of the procedure a problem?	1 (no) to 10 (very)	3 (3)
Did you find it difficult to stay still for the procedure?	1 (no) to 10 (very)	2 (2)
How did the procedure compare to your expectations?	1 (worse) to 10 (better)	7 (4)
How did you find the procedure overall?	1 (not unpleasant) to 10 (very unpleasant)	3 (3)
Would you have the procedure again?	1 (I wouldn't mind) to 10 (I would mind)	3 (3)

A positive response was defined as a given score of 1 to 5, and a negative response as 6 to 10 (reversed for question 7).

A pooled analysis of the patient satisfaction questionnaire results showed that 75% of respondents were positive ($p<0.05$) about GAE as a treatment for knee osteoarthritis

Change in analgesia (32 patients having GAE)

	Baseline	**3 months**	**1 year**
Number of patients having paracetamol	8	7	4
Number of patients having NSAIDs	10	5	4
Number of patients having opiates	4	3	3

Key safety findings

Mild self-limiting skin discoloration over the embolised territory (grade 3): n=4. This was caused by non-target cutaneous embolisation and completely resolved within 3 weeks.

Small self-limiting groin haematoma (grade 2): n=1

From the 16 patients completing 1-year follow up, there were no cases of osteonecrosis of the knee joint detected on MRI.

Study 6 Casadaban LC (2020)

Study details

Study type	**Systematic review**
Country	Okuno (2017) in Japan; Bagla (2020) in US; Lee (2019) in Korea
Recruitment period	Publication date: 2017 to 2020
Study population and number	n=133 (186 knees; 3 studies) Patients with osteoarthritis-related knee pain
Age and sex	Mean 65 years; 70% female BMI: mean 26 kilograms per square metre
Patient selection criteria	Inclusion criteria: patients with knee osteoarthritis, having GAE, with any or no comparison groups, and clinical outcomes such as pain scores and adverse events. Exclusion criteria: studies of hemarthrosis, review articles or republished data in the case of already-included patients.
Technique	GAE: A total of 186 knees in 133 patients were embolized with 0.5 g IPM/CS (159/186, 85%) or 75 or 100 µm embozene (27/186, 15%).
Follow-up	2 years
Conflict of interest/source of funding	None

Analysis

Study design issues: This systematic and qualitative review summarised the current literature on GAE as a treatment for osteoarthritis-related knee pain. Technical success was defined as embolisation of at least 1 genicular artery.

Four online databases were searched. Two reviewers independently screened all the articles according to predefined inclusion and exclusion criteria, and disagreements were resolved by consensus. They also independently extracted data. When necessary, the VAS was converted from a 0 to 10 scale to a 100-mm scale. Both total and subset WOMAC scores were recorded for analysis (global score range 0 to 96). MRI findings according to the WORMS system were also recorded when available. Adverse events were graded according to Society of Interventional Radiology (SIR) or CIRSE classification system.

Knee treatments across studies were aggregated and then separated by embolic material used, either IPM/CS or Embozene, to compare pain score outcomes and adverse events. Lack of patient-level data across all studies precluded rigorous meta-analysis.

Study population issues: This review included studies 1 to 3 (Okuno 2017; Bagla 2020; Lee 2019). All 3 included studies were cohort studies without control groups; as a summary of level 2 evidence, this review was also level 2. A total of 133 patients including 53 bilateral treatments with mild-to-moderate (174/186, 94%) or severe (12/186, 6%) osteoarthritis resistant to conservative therapy underwent GAE.

Key efficacy findings

Number of patients analysed: 133 (186 knees)

Baseline and treatment characteristics

Characteristic	Okuno et al. (2017)	Lee et al. (2019)	Bagla et al. (2020)	Total
Number of patients	72	41	20	133
Number of knees treated (right/left)	95 (49/46)	71 (35/36)	20 (11/9)	186 (95/91)
Vessels treated per knee	3.2	Not reported	2.5	-
MRI performed	95 knees in 72 patients	12 patients	20 patients	78% (104/133)
MORMS synovitis score baseline	1.52[a]	Not reported	Not reported	-
After 2 years	0.72[a]	-	-	-
Type of embolisation				
IPM/CS	88 knees, 65 patients	71 knees, 41 patients	0	85% (159/186)
75 to 100 µm Embozene	7 knees in 7 patients	0	20 knees in 20 patients	15% (27/186)
Neovascularisation on angiography	100%	100%	100%	100%
Technical success	100%	100%	100%	100%
Subsequent GAE procedure	13 knees	Not reported	Not reported	-
NSAIDS usage at baseline	54% (39/72)	78% (46/59)[b]	65% (13/20)	65% (98/151)
After 6 months	8% (6/72)	25% (15/59)[b]	30% (6/20)	18% (27/151)

[a]Reported in 35 knees in 29 patients

[b]Mild-to-moderate osteoarthritis group only

VAS: Average VAS across all studies decreased from baseline at 1 day, 1 week, 1 month, 3 months, 4 months, 6 months, 1 year and 2 years (66.5 at baseline compared with 33.5, 32.7, 33.8, 28.9, 29.0, 22.3, 14.8 and 14.0, respectively). In each study, this was statistically significant.

WOMAC: Total WOMAC scores were reported in 2 studies and subset scores in 1 study. Average total WOMAC scores decreased from baseline at 1, 3, 4, 6, 12 and 24 months (45.7 at baseline compared with 24.0, 31.0, 14.8, 14.6, 8.2 and 6.2, respectively).

Comparison of embolic material groups: Cumulative data across all studies after removing severe osteoarthritis cases (n=12) were separated by type of embolic material used, either IPM/CS (147/174, 84%) or Embozene (27/174, 16%). Qualitatively, the embozene cohort had a greater mean decrease in VAS at 1 month compared

to the IPM/CS cohort (mean decrease: 48.8 mm compared with 30.8 mm); however, these two cohort outcomes became more similar by 6 months (47.1 mm compared with 46.2 mm).

This qualitative trend was similar for WOMAC scores reported in 115 treatments (Embozene used in 27/115, 23%) at 1 month (mean decrease: 32.2 compared with 18.5), which became more similar at 6 months (30.0 compared with 31.3).

Key safety findings

No major adverse events were reported.

Minor adverse events (SIR class A or B, CIRSE grade 1 or 2)

	Okuno et al. (2017)	Lee et al. (2019)	Bagla et al. (2020)	Total
Puncture-site haematoma	17% (12/72)	12% (5/41)	5% (1/20)	10% (18/186)
Transient skin changes/erythema	57% (4/7)[c]	10% (4/41)	65% (13/20)	11% (21/186)[d]
Fever	-	2% (1/41)	-	0.5% (1/186)
Paraesthesia	-	-	10% (2/20)	1% (2/186)

[c]Embozene patients only
[d]All events resolved without intervention. These occurred disproportionately in 17/27 (63%) of embozene cases and lasted 1 to 3 months, but only in 4/159 (2.5%) of IPM/CS cases and lasted about 3 weeks.

Validity and generalisability of the studies

- Of the 5 case series, 4 were prospective (Okuno 2017; Bagla 2020; Landers 2020; Little 2021) and 1 was retrospective (Lee 2019).
- Studies were conducted in various countries, including Australia, Japan, Korea, UK and US.
- Mean age ranged from 59 to 67 years and patients were more likely to be female.
- The follow-up periods ranged from 6 months to 4 years, and losses to follow up were 4 patients in Okuno (2017) and withdrawals were 2 patients in Landers (2020).
- Casadaban (2020) included Okuno (2017), Bagla (2020) and Lee (2019) but the total sample of 181 patients derived from removing duplications.
- Patients with persistent knee pain for 3 months or more were included but variation existed in terms of the severity of knee pain (ranged from mild to severe) and osteoarthritis (ranged from mild to severe).
- The size of embolic particles and different embolic materials (such as IPM/CS, embozene, embosphere, and polyvinyl) used might affect efficacy and safety profiles.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Platelet-rich plasma injections for knee osteoarthritis. NICE interventional procedures guidance 637 (2019). Available from https://www.nice.org.uk/guidance/ipg637

- Joint distraction for knee osteoarthritis without alignment correction. NICE interventional procedures guidance 529 (2015). Available from https://www.nice.org.uk/guidance/ipg529

- Implantation of a shock or load absorber for mild to moderate symptomatic medial knee osteoarthritis. NICE interventional procedures guidance 512 (2015). Available from https://www.nice.org.uk/guidance/ipg512

- Individually magnetic resonance imaging-designed unicompartmental interpositional implant insertion for osteoarthritis of the knee. NICE interventional procedures guidance 317 (2009). Available from https://www.nice.org.uk/guidance/ipg317

- Arthroscopic knee washout, with or without debridement, for the treatment of osteoarthritis. NICE interventional procedures guidance 230 (2007). Available from https://www.nice.org.uk/guidance/ipg230

NICE guidelines

- Osteoarthritis: care and management. NICE clinical guideline 177 (2014, updated in 2020). Available from https://www.nice.org.uk/guidance/cg177

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaire for genicular artery embolisation for pain from knee osteoarthritis was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE did not receive any completed submissions.

Issues for consideration by IPAC

Ongoing trials:

- Geniculate artery embolisation for knee osteoarthritis (GAEKO). NCT03835988. Single group assignment. Estimated enrolment: 20 patients. Estimated completion date: December 2021. Canada.
- Novel transcatheter arterial embolization for treatment of knee osteoarthritis: a randomized sham-controlled clinical trial. NCT03884049. RCT. Estimated enrolment: 58 patients. Estimated completion date: November 2021. Netherlands.
- Safety and Efficacy of Genicular Artery Embolization for the Treatment of Symptomatic Knee Osteoarthritis. NCT03491397. Single group assignment. Estimated enrolment: 40 patients. Estimated completion date: June 2021. US.
- Randomized Placebo-Controlled Single Blinded Study of Geniculate Artery Embolization for Knee Pain Secondary to Osteoarthritis. NCT03362957. RCT. Recruitment completed: 21 patients. Actual completion date: April 2020. US. Under review.
- Evaluating transcatheter arterial embolisation for improvement of pain in OA of the knee – a randomised controlled trial. ACTRN12616001184460. RCT. Estimated enrolment: 58 patients. Estimated completion date: August 2021. Australia.
- Phase II trial of transcatheter arterial micro-embolisation for refractory chronic knee pain: multicentre study (PATRICK study). (JPRN-UMIN000023442). Single arm. Recruitment completed: 55 patients. Japan.

References

1. Okuno Y, Korchi AM, Shinjo T et al. (2017) Midterm clinical outcomes and mr imaging changes after transcatheter arterial embolisation as a treatment for mild to moderate radiographic knee osteoarthritis resistant to conservative treatment. Journal of vascular and interventional radiology : JVIR 28(7): 995-1002
2. Bagla S, Piechowiak R, Hartman T et al. (2020) Genicular artery embolization for the treatment of knee pain secondary to osteoarthritis. Journal of vascular and interventional radiology 31(7): 1096-102
3. Lee SH, Hwang JH, Kim DH et al. (2019) Clinical outcomes of transcatheter arterial embolisation for chronic knee pain: mild-to-moderate versus severe knee osteoarthritis. Cardiovascular and interventional radiology 42(11): 1530-6
4. Landers S, Hely R, Page R et al. (2020) Genicular artery embolisation to improve pain and function in early-stage knee osteoarthritis-24-month pilot study results. Journal of Vascular and Interventional Radiology 31(9): 1453-8
5. Little MW, Gibson M, Briggs J et al. (2020) Genicular artery embolisation in patients with osteoarthritis of the knee (GENESIS) using permanent microspheres: Interim analysis. Cardiovasc Intervent Radiol
6. Casadaban LC, Mandell JC and Epelboym Y (2020) Genicular artery embolisation for osteoarthritis related knee pain: a systematic review and qualitative analysis of clinical outcomes. CardioVascular and Interventional Radiology

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	24/11/2020	Issue 11 of 12, November 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	24/11/2020	Issue 11 of 12, November 2020
International HTA database	24/11/2020	-
MEDLINE (Ovid)	24/11/2020	1946 to November 23, 2020
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	24/11/2020	1946 to November 23, 2020
EMBASE (Ovid)	24/11/2020	1974 to 2020 Week 47

Trial sources searched 2 March 2020

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 2 March 2020

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Number	Search term
1	Embolization, Therapeutic/
2	Embolism/
3	Embolotherap*.tw.
4	(Genicul* or GAE or neovessel*).tw.
5	(transcathet* adj4 (arter* or genicula*) adj4 emboli?at*).tw. (2370)
6	or/1-5
7	Osteoarthritis, Knee/
8	exp Knee Joint/ (
9	((knee* or patella* or meniscal* or articular* or patellofem*) adj4 (OA or osteoarthrit* or cartilag* or degenerat* or diseas* or deteriorat* or injur* or defect*)).tw.
10	Gonarthrosis*.tw.
11	((knee* or patella* or meniscal* or articular* or patellofem*) adj4 (degenerativ* adj4 arthriti*)).tw.
12	or/7-11
13	6 and 12
14	Embosphere Microspheres.tw
15	EmboGold Microspheres.tw.
16	Embozene Microspheres.tw.
17	or/14-16
18	13 or 17
19	Animals/ not Humans/
20	18 not 19

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Choi JW, Ro DH, Chae HD et al. (2020) The value of preprocedural MR imaging in genicular artery embolization for patients with osteoarthritic knee pain. Journal of Vascular and Interventional Radiology	Case series n=18 (28 knees)	Large bone marrow lesions and severe meniscal injuries on MR imaging, as well as high KL grades, indicated poor responses to GAE.	This study assessed the value of preprocedural MR imaging in GAE for patients with osteoarthritic knee pain. Limited efficacy and safety data were reported.
Goldman DT, Piechowiak R, Nissman D et al. (2018) Current concepts and future directions of minimally invasive treatment for knee pain. Current rheumatology reports 20(9): 54	Review	Evaluation of genicular artery embolisation is still in the early phases, but initial results warrant further study.	Review article
Lauko K, Tangchaiburana S and Padia SA (2020) Transarterial genicular artery embolization as treatment of painful knee osteoarthritis in a 64-year-old woman. Journal of Radiology Nursing 39(2): 89-91	Case report n=1 (64 years; female)	Genicular artery embolisation is a safe and promising procedure offered by Interventional Radiology that requires only moderate sedation and has minimal recovery time.	Single case report

Okuno Y, Korchi AM, Shinjo T et al. (2015) Transcatheter arterial embolisation as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. Cardiovascular and interventional radiology 38(2): 336-43	Non-randomised comparative study n=14 (IPM/CS in 11 patients compared with 75 µm Embozene microsphere in 3 patients)	Transcatheter arterial embolisation for mild to moderate knee osteoarthritis was feasible, rapidly relieved resistant pain and restored knee function.	Sample was included in Okuno (2017)
Sajan A, Bagla S and Isaacson A (2020) Non-neoplastic disease outside the spine-genicular artery embolisation and adhesive capsulitis embolization. Techniques in Vascular and Interventional Radiology: 100702	Review	Initial research into the treatment of pain secondary to knee osteoarthritis and shoulder adhesive capsulitis with embolisation have yielded promising results. With further investigation, embolisation may become a mainstay of treatment for pain from these conditions	Review article