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REVIEW

Genicular Artery Embolization for Osteoarthritis Related Knee Pain: A Systematic Review and Qualitative Analysis of Clinical Outcomes

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Abstract *Objective* To systematically review the published literature on genicular artery embolization (GAE) for osteoarthritis (OA) related knee pain. *Materials and Methods* Using three databases, a systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Outcome measures included the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Results* Three single-arm studies were included from an initial search yielding 305 results. One hundred and eighty-six knees in 133 patients with either mild-to-moderate (174/186, 94%) or severe (12/186, 6%) OA underwent embolization with either imipenem/cilastatin sodium (159/186, 85%) or embozene (27/186, 15%). Technical success was 100%. Average VAS improved from baseline at 1 day, 1 week, 1 month, 3 months, 4 months, 6 months, 1 year and 2 years (66.5 at baseline vs 33.5, 32.7, 33.8, 28.9, 29.0, 22.3, 14.8 and 14.0, respectively). Average WOMAC scores improved from baseline at 1, 3, 4, 6, 12 and 24 months (45.7 at baseline vs 24.0, 31.0, 14.8, 14.6, 8.2 and 6.2). Severe OA in 12 cases showed initially improved VAS, but was not sustained. Minor adverse events such as erythema in the region of embolization (21/186, 11%), puncture-site hematoma (18/186, 10%), paresthesia (2/186, 1%) and fever (1/186, 0.5%) were reported. *Conclusion* Limited single-arm studies report GAE is promising for treating OA-related pain. Most treatments performed for mild-to-moderate OA demonstrated durable clinical responses from 6 months to 4 years. Limited data for severe OA suggest a non-durable response. Future studies should be standardized to facilitate comparison and control for placebo effect.

Keywords Genicular artery embolization · Interventional radiology · Osteoarthritis

Introduction

Symptomatic knee osteoarthritis (OA) affects more than 1 in 10 adults based on National Consensus data (NHANES III) and is a leading cause of disability [1, 2]. The cause of knee OA is multifactorial and pain can persist despite medical and surgical treatments [3, 4]. In conjunction with cartilage breakdown, literature suggests that chronic bone and synovial inflammation stimulates angiogenesis, hyperplasia and ongoing recruitment of inflammatory cells that leads to sensory nerve growth, which contributes to pain [5–8]. Okuno et al. first described treatment of angiographically abnormal vasculature associated with areas of osteoarthritic knee pain by percutaneous embolization with a non-permanent agent, imipenem/cilastatin sodium (IPM/CS), or permanent embolic, embozene (Varian Medical Systems, Palo Alto, CA) microspheres, based on experience from treating chronic musculoskeletal pain for tendinopathy and adhesive capsulitis [9, 10]. The group then published results showing reduced pain scores following treatment of 14

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patients for mild-to-moderate knee OA [11]. Since then, this group and others have further published on treating knee OA with genicular artery embolization (GAE). This systematic and qualitative review aims to summarize the current literature on GAE as a treatment for OA-related knee pain.

Materials and Methods

Search Strategy and Study Selection

Three online databases (Embase, PubMed, and Web of Science) were searched from inception to December 16, 2019. Institution Review Board (IRB) approval was not needed as this study was limited to published data. Using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, all fields were searched for: (geniculate OR genicular OR knee) AND (embolization OR percutaneous OR transcatheter) AND (osteoarthritis). Reports were evaluated using PICO (Population, Intervention, Comparison and Outcomes). Inclusion criteria included a population of patients with knee OA, undergoing GAE, with any or no comparison groups, and clinical outcomes such as pain scores and adverse events [12]. Exclusion criteria included studies of hemarthrosis, review articles, or republished data in the case of already-included patients. All studies were screened by 2 of the investigators independently, first by study title, and from those the abstracts were reviewed, followed by a full-text review to select the final cohort. Disagreements were resolved by consensus. Lastly, a hand search of the references of the included studies was performed. Studies were evaluated by level of evidence according to the Oxford Centre for Evidence-based Medicine [13].

Data Extraction

Relevant demographic, clinical, procedure-related, outcome and adverse event data from each study were independently abstracted and organized in Microsoft Excel (Microsoft, Redmond, WA). When necessary, the Visual Analogue Scale (VAS) was converted from a 0 to 10 scale to a 100-mm scale. Both total and subset Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores were recorded for analysis (global score range, 0–96). MRI findings according to the Whole-Organ Magnetic Resonance Scoring (WORMS) system were also recorded when available. Adverse events were graded according to Society of Interventional Radiology (SIR) or Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Classification System [14, 15]. An attempt was made to contact the authors of the included studies for patient-level data, as well as three clinical groups with active unpublished clinical trials listed on clinicaltrials.gov by email, but no additional data were provided for analysis.

Statistical Analysis and Quality Assessment

Inter-reader agreement k statistic was calculated at each stage of study selection: k 0.00 to 0.20 for slight agreement; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.00, almost perfect agreement. The remainder of the analysis was descriptive in nature. Statistical analysis was performed using Stata SE 12.0 (College Station, TX). Study quality was assessed according to the level of evidence on a Level I through V system [16].

Qualitative Analysis of Type of Embolic Material

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. Severe osteoarthritis (Kellgren–Lawrence (KL) grade 4) cases were analyzed separately as this was unique to one study.

Results

Systematic Search

The initial search yielded 305 studies after duplicates were removed. After screening titles, abstracts and the full text, three studies met the inclusion and exclusion criteria for this study (Fig. 1). The inter-reader agreement at the title review stage was $k = 0.397$ (fair), abstract stage was $k = 0.732$ (substantial), and full-text review stage was $k = 1.00$ (perfect).

Study Characteristics

Three full-length reports without control groups were published between 2017 and 2019 from three countries [17–19]. Inclusion criteria included persistent knee pain refractory to conservative treatment for over 3 months and osteoarthritis on weight-bearing knee radiograph. Patients continued medical management after the procedure. Two studies required VAS persistently above 50 mm, while one required a score greater than 2 on a 10-point VAS. Exclusion criteria varied, but generally contained local infection, malignancy, advanced atherosclerosis, rheumatoid arthritis, age under 40, and previous knee surgery. Knee magnetic resonance (MR) imaging was performed in

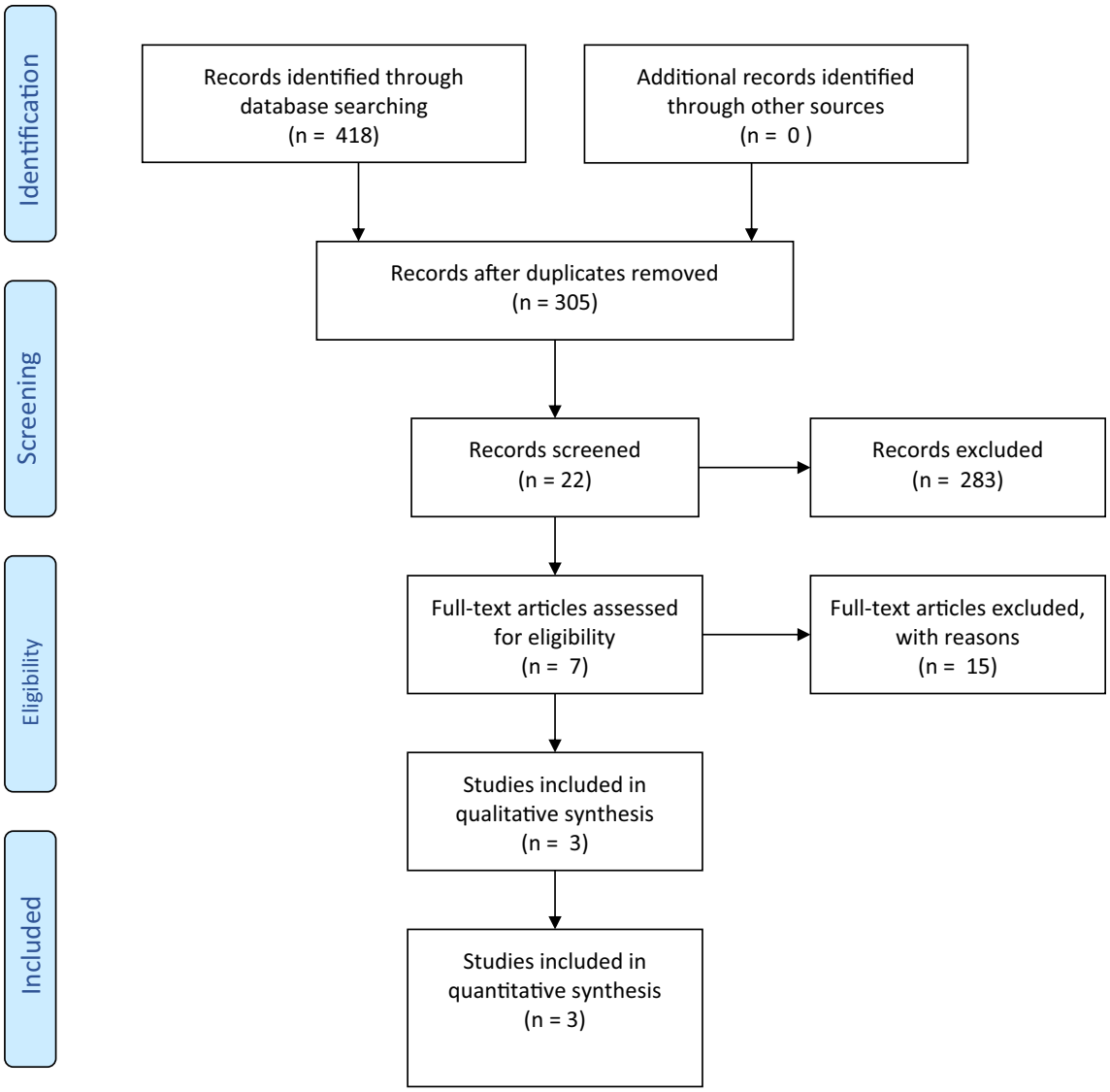

Fig. 1 Flow diagram of systematic review search results

the majority of cases pre-procedure. One study included severe osteoarthritis if the patient could not undergo general anesthesia or did not want total knee arthroplasty, while the remaining studies limited inclusion to mild–moderate OA.

Study Quality

All three included studies were cohort studies without control groups; as a summary of Level II evidence, our study is also Level II. Only one study reported data metrics for patient selection and non-inclusion. Thus, a formal assessment of study selection bias was not performed. A meta-analysis was not performed because of lack of patient-level data in all studies. Therefore, a systematic review and qualitative analysis was performed.

Patient demographic and clinical characteristics.

A total of 133 patients including 53 bilateral treatments with mild-to-moderate (174/186, 94%) or severe (12/186, 6%) OA resistant to conservative therapy underwent GAE (Table 1). In all studies, patients were more likely to be female.

Genicular Artery Embolization Procedure

A total of 186 knees in 133 patients were embolized with either 0.5 g IPM/CS (159/186, 85%) or 75 or 100 µm embozene (27/186, 15%). Ipsilateral antegrade femoral artery access was performed using either a 3-French or 4-French sheath in two studies. Contralateral arterial access with a 6-French sheath was obtained in the third study. Two studies administered 2000 IU heparin. Either a

Table 1 Patient demographic and treatment characteristics

Characteristic	Okuno et al. (2017) [18]	Lee et al. (2019) [19]	Bagla et al. (2020) [17]	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)
Gender, as percent female	68%	76%	55%	70%
Age, mean (range)	64 (44–79)	67 (47–80)	62 (49–84)	65 (44–84)
BMI in kg/m^2	25.1	24.9	35.0	26.0
Osteoarthritis (OA) severity				
Mild–moderate (KL grade 1–3)	95 (100%)	59 (83%)	20 (100%)	174/186 (94%)
Severe (KL grade 4)	0	12 (17%)	0	12/186 (6%)
Vessels treated per knee	3.2	Not reported	2.5	–
Superior patellar artery	32 (8%)	–	–	–
Descending genicular artery	84 (21%)	–	–	–
Lateral superior genicular arteries	52 (13%)	–	–	–
Lateral inferior genicular arteries	75 (19%)			
Median genicular artery	30 (8%)	–	–	–
Medial superior genicular arteries	26 (7%)	–	–	–
Medial inferior genicular arteries	74 (19%)			
Anterior tibial recurrent artery	18 (5%)	–	–	–
MRI performed	95 knees in 72 patients	12 patients	20 patients	104/133 (78%)
WORMS synovitis score baseline	1.52[a]	Not reported	Not reported	–
After 2 years	0.72[a]	–	–	–
Type of embolization				
Imipenem/cilastatin sodium	88 knees, 65 patients	71 knees, 41 patients	0	159/186 (85%)
75–100 μm embozene	7 knees in 7 patients	0	20 knees in 20 patients	27/186 (15%)
Neovascularization 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	39/72 (54%)	46/59 (78%)[b]	13/20 (65%)	98/151 (65%)
After 6-months	6/72 (8%)	15/59 (25%)[b]	6/20 (30%)	27/151 (18%)
Adverse events				
Puncture-site hematoma	12/72 (17%)	5/41 (12%)	1/20 (5%)	18/186 (10%)
Transient skin changes/erythema	4/7 (57%)[c]	4/41 (10%)	13/20 (65%)	21/186 (11%)
Fever	–	1/41 (2%)	–	1/186 (0.5%)
Paresthesia	–	–	2/20 (10%)	2/186 (1%)

[a]Reported in 35 knees in 29 patients

[b]Mild-to-Moderate OA group only

[c]Embozene patients only

3-French angiographic catheter or a 1.7-, 2.0-, or 2.4-French microcatheter was used to select the target genicular vessels to identify abnormal staining or blush-type enhancement on the arterial phase, which correlated with the site of reported pain. Embolic material diluted with iodinated contrast was administered in small increments until there was reduced abnormal vessel filling and blush in two studies, or until "flow was stagnated" in the third study. On average, 2–3 vessels were treated per knee (Table 1; Fig. 2). Hemostasis was achieved using manual compression in the largest study, a closure device in the second largest study, and was not reported in the third study. All treatments were technically successful as defined as embolization of at least one genicular artery.

Clinical Outcomes

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 vs 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 (Fig. 3). Total WOMAC

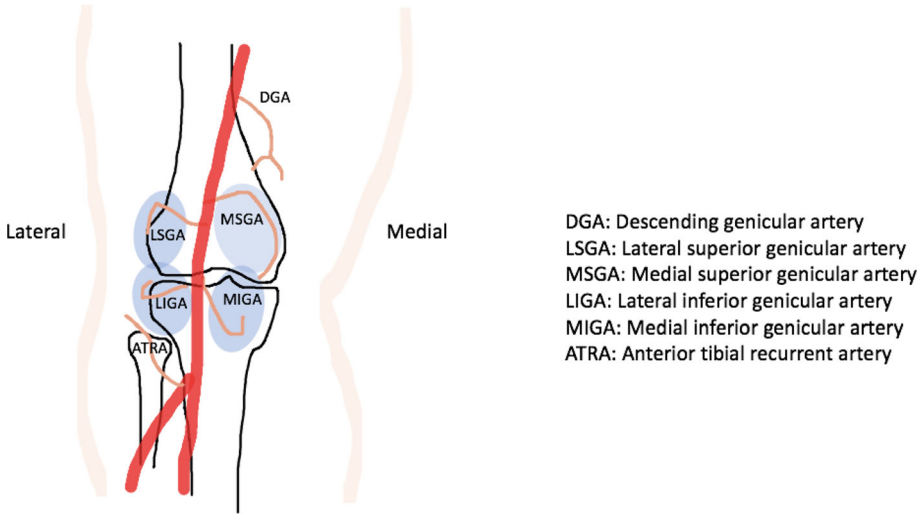

Fig. 2 Diagram of the anatomic distribution and typical branching pattern of the genicular arteries of the knee

scores were reported in two studies, and subset scores in 1 study (Fig. 4). Average total WOMAC pain scores decreased from baseline at 1, 3, 4, 6, 12 and 24 months (45.7 at baseline vs 24.0, 31.0, 14.8, 14.6, 8.2 and 6.2). Okuno et al. described intent-to-treat clinical success at 6-months as 86.3% (including four patients lost to follow-up classified as clinical failure), by pain greater than 50% of baseline WOMAC score persisting for 2 months. KL grade 1/2 OA had 85.2% estimated cumulative clinical success at 2 years on Kaplan-Meier analysis compared to 69.8% for KL grade 3 OA (with overlapping 95% confidence intervals). 13/95 (14%) cases from that study underwent a second procedure for persistent or recurrent pain. Lee et al. demonstrated clinical success in all mild-to-moderate OA treatments at 3 months, maintained for a mean 10 months (range 6–19 months), defined by 50% decrease in VAS. Bagla et al. reported 85% clinical success at 6 months defined by 20% reduction in VAS, and 80% defined by 16% reduction in WOMAC total score. All three studies noted a decrease in conservative therapy use following embolization (between 65% and 100%); however, there was heterogeneity in reporting for NSAIDs (three studies), opiates (two studies), hyaluronic acid injections (two studies), acetaminophen (one study), and physical therapy (one study). Only NSAIDs use at baseline and 6 months after the procedure was reported uniformly (Table 1).

Severe OA Subgroup

A subgroup of 12 patients with severe OA from one study showed significantly improved average VAS initially after treatment (P = <0.01 at 1-month), but this was not sustained at 3 or 6 months (6.3 at baseline vs 4.1, 4.1, 4.4, 5.4 and 5.9 at 1 day, 1 week, 1 month, 3 months and 6 months). Individual patient data were not reported to ascertain if any individuals had a sustained response.

MRI Imaging Follow-Up

While 104/133 (78%) patients underwent an MRI, only one study characterized MRI imaging features before and after

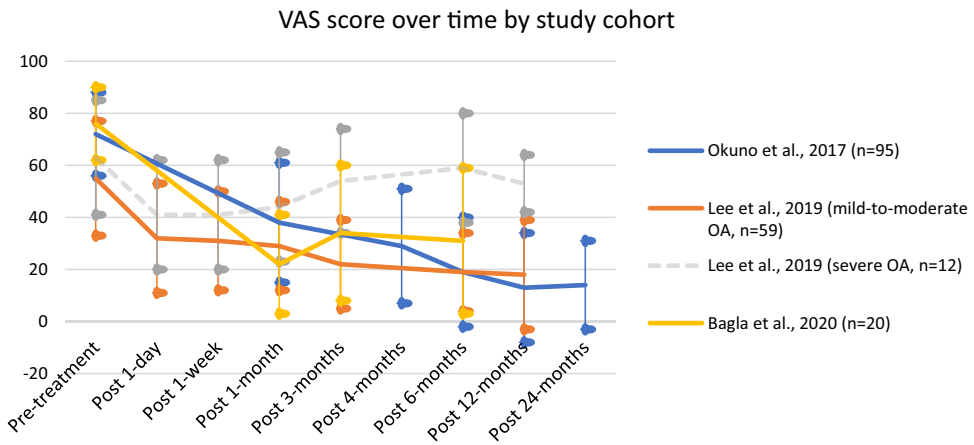

Fig. 3 VAS score over time by study cohort

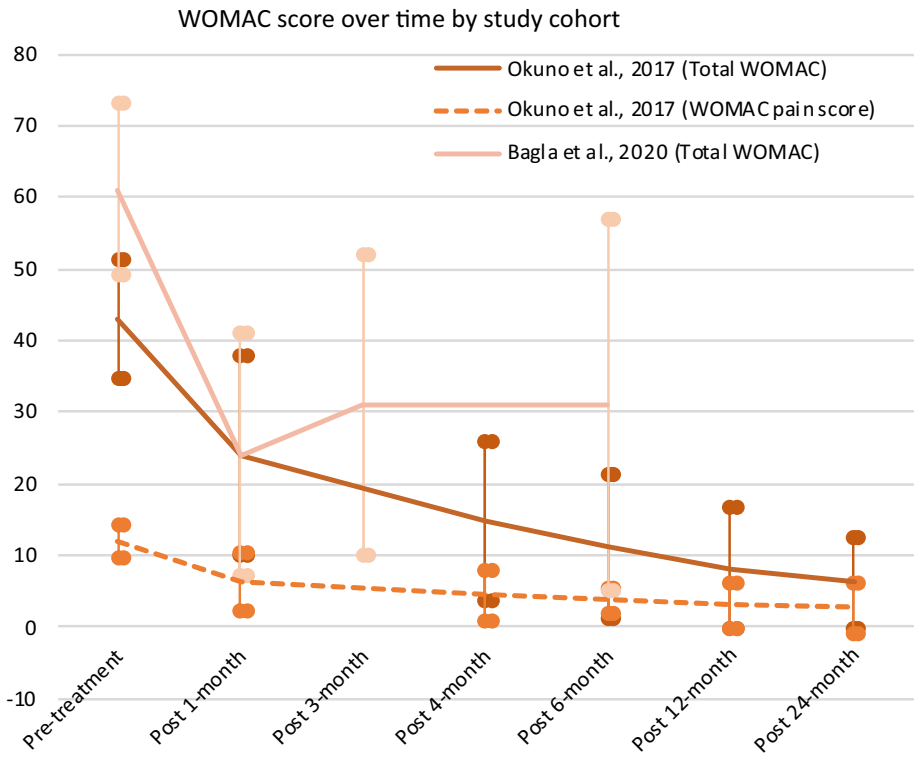

Fig. 4 WOMAC score over time by study cohort

the procedure in a subset of patients using the WORMS score. Okuno et al. reported 35 knees in 29 patients had a statistically significant decrease in WORMS synovitis score at 2 years (1.52 at baseline vs 0.72 at 2-years, $p = 0.0016$), though other subset and total WORMS score were similar. Bagla et al. noted a small (<2 cm) focus of non-specific bone marrow edema or inflammation in two patients on follow-up; they did not undergo further treatment or follow-up as they were asymptomatic.

Adverse Events

No major adverse events were reported. The most common minor (SIR class A or B, CIRSE grade 1 or 2) adverse event was skin changes including transient erythema in the region of embolization without ulceration in a cumulative of 21/186 (11%) of treatments and resolved in all cases without intervention. Notably, these occurred disproportionately in 17/27 (63%) of embozene cases and lasted 1–3 months, but only in 4/159 (2.5%) of IPM/CS cases and lasted about 3 weeks. Puncture-site hematoma or hemorrhage occurred in 18/186, (10%) and resolved within 1–3 weeks. Bagla et al. reported great toe and plantar paresthesia in two cases that resolved in 2 weeks. Lee et al. reported a single fever that subsided in 1 day (1/186, 0.5%).

Comparison of Embolic Material Groups

Only one study reported a non-randomized comparison between IPM/CS and 75 µm embozene embolic material. Okuno et al. described no difference in clinical success at 6 months ($P = 1.000$). Cumulative data across all studies after removing severe OA cases ($n = 12$) were separated by type of embolic material used, either IPM/CS (147/174, 84%) or Embozene ($n = 27/174$, 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 vs. 30.8 mm); however, these two cohort outcomes became more similar by 6 months (47.1 mm vs. 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 vs. 18.5), which became more similar at 6 months (30.0 vs. 31.3). Formal statistical comparison between two cohorts was not feasible due to lack of individual treatment data.

Discussion

Genicular arterial embolization is an established treatment for hemarthrosis after total knee arthroplasty, but recently has been applied to the treatment of osteoarthritis related knee pain [11, 20]. The rationale is that knee osteoarthritis caused by a chronic cycle of synovial inflammation,

cartilage breakdown, subchondral bone remodeling and eventual angiogenesis leads to new nerve growth that contributes to knee pain; embolizing the angiographically hyperemic vessels of the affected knee may reduce the transport of proinflammatory and catabolic mediators and decrease stimulation of sensory nerves [5–8]. In the past 2 years, three groups from Japan, China, and USA have published results of 186 GAE treatments for osteoarthritis [17–19]. This systematic review summarizes clinical and imaging outcomes, patient characteristics, treatment protocols, and adverse events to create a framework for standardizing future studies.

All three studies describe GAE as safe and effective for OA-related knee pain, with 80–100% clinical success, defined by 20–50% reduction in pain scores persisting for at least 6 months to 4 years post-procedure. Average treatment response was seen as early as 1-day and 1-month post-procedure, with only minimal further improvement through 1- and 2-years post-procedure, suggesting that early outcomes may correlate with maximal treatment response in many cases.

While these are promising preliminary results, comparison between studies is challenging because of heterogeneous inclusion criteria, variable embolics, and variable outcome measurements and definitions of clinical success. For example, Lee et al. included patients with a lower pain score threshold compared to the other studies, which may impact results. Additionally, they included a subset of severe knee OA cases that did not show durable treatment response at 3–6 months, leading the authors to conclude that GAE has a limited role for severe OA. They hypothesized that this could be due to mechanical factors of bone-on-bone contact that persist after the procedure, contributing to ongoing subchondral bone degeneration, inflammation and continued pain [19].

The primary embolic agent used in two of the studies was an antibiotic crystal mixture (IPM/CS) that forms particles when mixed with iodinated contrast that has a demonstrated transient embolic effect with particle size approximately 10 to 70 μm [21]. The literature describes it as an embolic agent for tumor embolization, gastrointestinal bleeding and musculoskeletal pain [9, 10, 21, 22]. In contrast, a permanent embolic agent, Embozene microspheres with size of 75–100 μm were used exclusively by Bagla et al. and secondarily by Okuno et al. Based on the single study which treated with both embolics, there was no difference in clinical success at 6 months [18]. In the current analysis, there was a more substantial qualitative decrease in pain scores at 1 month in the embozene cohorts compared to IPM/CS cohort, but this difference was not maintained at 6 months. It should be noted, however, that formal statistical comparison of these groups could not be performed due to heterogeneity in the studies and lack of individual treatment data. More studies are needed to evaluate this in a larger cohort.

Outcome measures varied between studies, including the VAS score as 10-point versus 100-point score in millimeters, of which the latter is more fastidious. Two studies also used the WOMAC score, a self-administered questionnaire with 24 items in three subsections (5 for pain, 2 for stiffness and 17 for physical function) commonly used for hip and knee osteoarthritis. Both Okuno et al. and Bagla et al. reported total and subset WOMAC scores and found similar trends in both. Given this, the increased detail of total WOMAC scores may be better suited for assessing pain and functional outcomes in future studies. All three studies reported that MRI was performed in some patients, but only Okuno et al. compared imaging outcomes before and after 2 years using the WORMS system, which is a semi-quantitative assessment of 14 features found on knee MRI [23]. Interestingly, that study showed that only the WORMS synovitis sub-score was statistically significantly improved at 2 years. This offers insight into the proposed treatment effect from GAE and suggests that contrast-enhanced MRI could measure clinical response after treatment, but more studies are needed. Lastly, all three studies found decreased conservative therapy use following embolization; however, there was little consistency reporting among NSAIDs, opiates, hyaluronic acid injections, acetaminophen, and physical therapy.

Clinical success was measured at different time points and according to different criteria across the studies. This should be standardized to 50% reduction in pain scores, as was used in two of the three studies, and measured at 1 month, 3 months and 6 months, since early results appear to be durable.

The most common minor complication was transient skin erythema, which occurred more often and lasted longer when using embozene (63% and lasted 1–3 months) compared to IPM/CS (2.5% and lasted 3 weeks) across the three studies. This could be a result of the permanent embolic nature of embozene compared to the temporary embolic effect of IPM/CS particles, but more studies are warranted. An access site hematoma occurred rather frequently, in 10% of treatments; however, this may in part be explained by the use of intra-arterial heparin in two of the studies with the highest hematoma rates.

There are many limitations to this study. First, there are only a small number of studies with heterogeneity of inclusion criteria, treatment technique and outcome reporting. Only one study by Bagla et al. included patient selection metrics including screening failures. Thus, there is high risk for study selection bias with unclear exclusions in the other two studies. Additionally, a lack of patient level data in two of three studies precludes the ability to perform a formal meta-analysis to account for variations in

baseline characteristics. Few subjects had post-intervention imaging follow-up; however, MRI assessment can assist evaluation for persistent or resolution of synovitis. There was no comparison to a standard of care, or aspiration of joint fluid to assess for post-intervention changes in markers of inflammation, or measures of blood-based biomarkers related to osteoarthritis, pre- and post-intervention. Lastly, there were no comparisons to sham interventions, even though the impact of placebo interventions on knee pain has been previously demonstrated after arthroscopic meniscectomy versus sham intervention [24].

In conclusion, current data suggests that GAE holds promise as a treatment for osteoarthritis related knee pain but requires further investigation. Validated outcome measures such as the total WOMAC score should be uniformly adopted, and definitions of clinical success should be both clinically meaningful and measurable (i.e., 50% reduction in pain scores at 1 month, 3 months and 6 months). Furthermore, evidence of clinical success should be corroborated with MRI synovitis analysis to assess for interval changes in synovitis following embolization. Given that interpretation of current data is limited by heterogenous inclusion criteria and definitions of clinical success, subsequent research should address these limitations.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest.

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