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Transarterial Embolization for the Treatment of Chronic Musculoskeletal Pain: A Systematic Review of Indications, Safety, and Efficacy

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Objective. The study objective was to evaluate the safety and efficacy of transcatheter arterial "embolization" (TAE) in the treatment of chronic "musculoskeletal pain" refractory to standard therapy.

Methods. PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched for original research articles evaluating TAE in patients with musculoskeletal conditions from database inception to January 21, 2020. Search terms employed were as follows: "embolization", "pain", "knee osteoarthritis", joint replacement, epicondylitis, tenderness, inflammation, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), microspheres, Embozene, geniculate artery, neovascularity, transcatheter, embolic, imipenem/cilastatin sodium, angiogenesis, and "musculoskeletal". Studies involving particle "embolization" for painful musculoskeletal conditions were included. Studies of TAE for hemarthrosis or malignancy-related "musculoskeletal pain" were excluded.

Results. The primary search yielded 1,099 sources; 7 articles and 4 abstracts were included for data extraction. All were cohorts or case series, with low risk of bias and moderate to poor level of evidence. Heterogeneity between studies was high, precluding meta-analysis. The reviewed studies reported the safety and efficacy of TAE for the treatment of "knee osteoarthritis"; adhesive capsulitis of the shoulder; tendinopathy/enthesopathy of the knee, shoulder, elbow, and ankle; and cervical myalgia. All TAEs were reported as technically successful without major complications or subsequent serious adverse events, including no reported osteonecrosis, cutaneous ulceration, limb ischemia, cartilage degeneration, or myotendinous injury. TAE significantly reduced pain and improved function for all of the treated conditions, with durable response up to 24 months post procedure.

Conclusion. TAE appears to be a safe and effective treatment for some types of chronic refractory "musculoskeletal pain". Randomized placebo-controlled studies are necessary to confirm these findings.

INTRODUCTION

"Musculoskeletal pain", most commonly due to osteoarthritis (OA), is a leading cause of disability in the United States. Unfortunately, many patients with chronic pain are unable to obtain adequate pain relief from pharmacologic therapies, or are not able to take these medications safely due to age or comorbidities (1).

Transcatheter arterial "embolization" (TAE) is a minimally invasive procedure performed by interventional radiologists. It is most commonly used to control bleeding, or to decrease the size of hypervascular tumors through selective "embolization" of small arteries (2–4). However, TAE techniques have recently been deployed to treat painful musculoskeletal conditions due to abnormally inflamed or hypervascular tissues. The underlying theory is that by blocking the vascular supply, the pathologic tissue will involute. This tissue will therefore no longer be a nociceptive trigger or produce pro-inflammatory mediators, and thus pain will resolve.

TAE is a novel intervention that could transform clinical care and shift the current paradigm for treating nonmalignant

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"musculoskeletal pain". There have been a number of small studies suggesting that TAE has an excellent safety and efficacy profile, but to date there are no definitive randomized controlled trials. To optimize understanding of existing data, we performed a systematic review of the use of TAE for "musculoskeletal pain" refractory to standard conservative therapies.

METHODS

Review design. This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Appendix 8) (5,6). The protocol was registered on the PROSPERO database (ID number 165083), an international database of prospectively registered systematic reviews with a health related outcome. See Appendix 2 for modifications and updates to the original protocol.

Search strategy and study eligibility. PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched, without language restrictions, for original research articles evaluating "embolization" in patients with musculoskeletal conditions from database inception to January 21, 2020. To ensure that we captured all studies using TAE, which may include novel indications, we included a broad list of search terms including combinations of the following: "embolization", "pain", "knee osteoarthritis", joint replacement, epicondylitis, tenderness, inflammation, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), microspheres, Embozene, geniculate artery, neovascularity, transcatheter, embolic, imipenem/cilastatin sodium, angiogenesis, and "musculoskeletal" (see Appendix 3 for details). An experienced research librarian provided guidance on designing the original search strategies. Reference lists of included articles were hand searched for additional sources, and the first and last authors of all included studies were hand searched in PubMed for potential additional sources (see Appendix 4 for search details).

Eligible studies included patients with musculoskeletal conditions who underwent intra-arterial particle "embolization" for the primary indication of improving pain. Studies using other "embolization" techniques (eg, coil "embolization") were excluded. Interim results were included if later analyses were unavailable. Studies evaluating intra-articular "embolization" for the primary indication of bleeding (eg, hemarthrosis) or tumor debulking were excluded. Studies of pediatric or animal subjects were also excluded. Randomized controlled trials, controlled trials, case-controlled studies, cohort studies, case series, and case reports were eligible. To ensure the review of all available data, published abstracts, conference papers, and unpublished papers were also eligible. While data were not extracted from review articles, reference lists from reviews were used to identify other potential sources of primary data. If articles reported on overlapping cohorts, the article with the largest sample size and/or longest duration of follow-up was included (see Figure 1).

Primary outcomes assessed included pain and adverse events. Other secondary clinical outcomes were included when available.

Study selection and data extraction. Two investigators (D.S. and M.M.) independently screened titles and abstracts. Two investigators (D.S. and S.K.) independently screened full texts of articles selected for review. Study de-duplication and management were performed using Covidence software (7). Two investigators (D.S. and S.K.) independently extracted data on study design, eligibility criteria, patient characteristics, outcomes measured, intervention details and embolic material used, adverse events, and clinical outcomes. Disagreements at any stage were resolved by consensus or adjudicated by a fourth investigator (L.A.M.).

Data analysis. Significant heterogeneity in clinical indications, embolic material used, and outcomes across the studies prevented valid combination of individual studies into a quantitative meta-analysis (see Table 1). Therefore, the evidence was qualitatively summarized by clinical indication, embolic material, and outcomes measured.

Evaluation of quality of evidence and quality assessment. Two investigators (L.A.M. and S.K.) independently evaluated the quality of the studies using a modified Newcastle-Ottawa Quality Assessment Scale for cohort studies (19,20). Two investigators (L.A.M. and S.K.) independently evaluated the quality of evidence for each study using a 5-point scale modified from the Oxford Centre for Evidence-Based Medicine (see Appendices 5 and 6) (21). Disagreements were resolved by consensus or adjudicated by a third investigator (D.S.). Because the aim of this review was to identify all data on TAE, no studies were excluded on the basis of quality.

RESULTS

The primary search resulted in 1,099 sources. After review, 7 papers and 4 abstracts were included for data extraction (see Table 1). The risk of bias was low for selection and moderate to low for outcomes (see Appendix 7). The quality of evidence was low because all studies were either unblinded cohorts or case series (see Appendix 6). There were no placebo controlled studies. TAE was used to treat different anatomic areas, including the knee, shoulder, elbow, and ankle, primarily for three different musculoskeletal conditions: OA, tendinopathy/enthesopathy, and adhesive capsulitis. One study evaluated TAE for chronic myalgia of the trapezius muscle (ie, cervical myalgia). The studies were from either Japan, South Korea, or the United States. All procedures were performed by an interventional radiologist. The standard definition of technical success of TAE includes angiography to visualize the vasculature, followed by selective catheterization of at least one artery supplying an area of abnormal hypervascularity, and transcatheter

delivery of an embolic agent until angiographic resolution of the hyperemic foci, with no complications. Results are presented stratified by the condition treated (see Appendix 8 for details).

Knee osteoarthritis. Three papers and one abstract evaluated TAE for the treatment of "knee osteoarthritis" (KOA), which involves embolizing the geniculate arteries. Two papers and one abstract reported data from studies performed in Asia, and one study was from the United States. All studies reported 100% technical success with no major adverse events. Minor complications included transient post-procedure cutaneous erythema without skin breakdown or ulceration, limited focal plantar paresthesia, and small self-resolving access site hematoma.

The largest study with the longest follow-up period was an open-label cohort study from a single center in Japan; 2-year outcomes were collected from consecutive TAE procedures performed on 95 knees in 72 patients at a single center in Japan (9). Patients had a mean age of 64 years and an average body mass index (BMI) of 25 kg/m^2. Prior to the procedure, all patients had moderate/severe pain (more than 50 of 100 mm on a Visual Analogue Scale [VAS]) and failure of at least 3 months of physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, intra-articular corticosteroid, and/or viscusupplemenation. Patients with Kellgren-Lawrence (KL) grade 4, prior knee arthroplasty, or rheumatoid arthritis were excluded. Of subjects, 65% were KL grade 1/2 and 35% were KL 3 with a mean pain duration of 29.7 months. Clinical success was defined as 50% reduction in WOMAC scores at 6 months relative to baseline, and clinical failure was defined as recurrence of pain to more than 50% of the baseline score lasting greater than 2 months. The authors reported clinical success in 86.3% (78%-92%) at 6 months, with no knees lost to follow-up. Of the 37 knees (39%) available for follow-up at 24 months, the success rate was 85.2% for KL 1/2 (72%-92%) and 69.8% for KL 3 (49%-84%). There was a clinically significant improvement in mean WOMAC and VAS scores compared with baseline at all study time points through 24 months. Baseline and 2-year magnetic resonance imaging (MRI) scores were available in 35 knees. Whole-Organ Magnetic Resonance Imaging Scores (WORMS) were performed, demonstrating a significant reduction in synovitis scores between baseline and

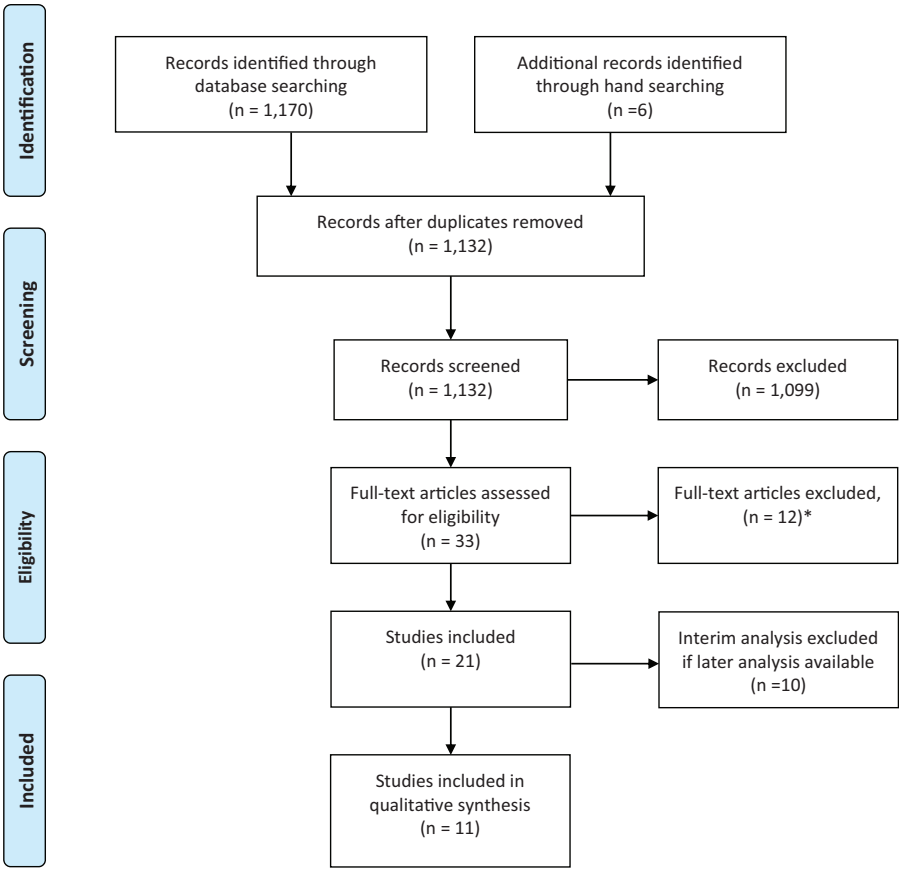

Figure 1. PRISMA 2009 Flow Diagram- Systematic Review of Embolization for Pain in Patients with Musculoskeletal Conditions
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
*Reasons for exclusion: review articles -6, description of clinical trial protocol-3, wrong outcome – outlining the anatomy of the knee -1, pelvic vein embolization -1,pediatric patients -1.

Table 1. Characteristics of included studies and summary of findings

Musculoskeletal Condition(s) Treated	Source	Age (Y)	Duration of Follow-Up (Mo)	Main Findings/Comments
Knee Osteoarthritis	Ref. 8 (Bagla et al, 2019; US) N = 20	Range: 49-84 Mean: 59.4	6	100% technical success 49% mean reduction in WOMAC and 59% mean reduction in VAS at 6 months 0% major adverse events (no osteonecrosis, cartilage, or tendon injury) Patient population with obesity (mean BMI: 35 kg/m^2)
	Ref. 9 (Okuno et al, 2017; Japan) N = 72 (95 joints)	Range: 44-79 Mean: 64.4	24	100% technical success 74% mean reduction in WOMAC and 74% mean reduction in VAS at 6 months 86% mean reduction in WOMAC and 81% mean reduction in VAS at 24 months 0% major adverse events MRI: significant reduction in synovitis at 24 months without osteonecrosis, tendinopathy, or cartilage loss
	Ref. 10 (Bhatia et al, 2019[a]; US and Japan) N = 21 (33 joints)	Range: 46-82 Mean cohort 1: 66 Mean cohort 2: 73	3	100% technical success 50% mean reduction in total WOMAC and 60% mean reduction in WOMAC pain score at 3 months 0% major adverse events No significant difference between administered IPM-CS and Embosphere embolic agent
	Ref. 11 (Lee et al, 2019; S. Korea) N = 41 (71 joints)	Range: 47-80 Mean: 67.2	6	100% technical success KL 1-3: 65% mean reduction in VAS at 3-6 months KL 4: 30% mean reduction in VAS at 1 month, but return to baseline at 3-6 months 0% major adverse events Longer baseline symptom duration in KL 4 patients
Lateral Epicondylitis (Elbow)	Ref. 12 (Okuno et al, 2019[a]; Japan) N = 52	Not reported	24	100% technical success 60% mean reduction in QuickDASH at 1 month, 90% reduction at 24 months 0% major adverse events MRI: improved tendinosis and tear scores without osteonecrosis, cartilage loss, or muscle atrophy
	Ref. 13 (Iwamoto et al, 2017; Japan) N = 24	Range: 34-66 Mean: 52.1	24	100% technical success 55% mean reduction in QuickDASH at 1 month, 90% reduction at 6 months 36% mean reduction in VAS at 1 month, 80% reduction at 6 months 38% mean reduction in PRTEE at 1 month, 88% reduction at 6 months 0% major adverse events 36% required second procedure
Trapezius Myalgia (Neck/Shoulder)	Ref. 14 (Shibuya et al, 2019[a]; Japan) N = 10	Range: 30-75 Mean: 61	6	30% mean reduction in BPI intensity and interference scores at 1 and 6 months 0% major adverse events
Adhesive Capsulitis (Shoulder)	Ref. 15 (Okuno et al, 2017; Japan) N = 25	Range: 39-68 Mean: 53.8	12	100% technical success 30% mean reduction in VAS at 1 week, 77% reduction at 3 months 42-degree mean increase in anterior elevation at 1 month, 88 degrees at 6 months 26-degree mean increase in external rotation at 1 month, 50 degrees at 6 months 53-point mean improvement in ASES at 1 month, 74-point improvement at 6 months 0% major adverse events, no humeral AVN Mean symptom duration at study entry: 7.7 months
Tendinopathy and Enthesopathy (Multiple Sites[b])	Ref. 16 (Okuno et al, 2013; Japan) N = 7	Range: 26-76 Mean: 51.7	4	100% technical success 78% mean reduction in VAS at 1 week, 87% mean reduction at 3 months 0% major adverse events (no digital ischemia, osteonecrosis, or tendon injury)

(Continued)

Table 1. (*Cont'd*)

Musculoskeletal Condition(s) Treated	Source	Age (Y)	Duration of Follow-Up (Mo)	Main Findings/Comments
Shoulder Tendinopathy and Elbow Tendinopathy	Ref. 17 (Hwang et al, 2018; S. Korea) N = 13 (15 joints)	Range: 27-75 Mean: 52.4	4	100% technical success 16% mean reduction in VAS at 1 week, 59% reduction at 4 months 73% mean reduction in VAS if positive enhancement on DSA at 4 months 30% mean reduction in VAS if negative enhancement on DSA at 4 months 0% major adverse events (no myotendinous injury)
	Ref. 18 (Min et al, 2019[a]; S. Korea) N = 24 (32 joints)	Not specified	4	100% technical success 29% mean reduction in VAS at 1 week, 61% mean reduction at 4 months 71% mean reduction in VAS if positive enhancement on DSA at 4 months 46% mean reduction in VAS if negative enhancement on DSA at 4 months 0% major adverse events (no myotendinous injury or digital ischemia)

Abbreviations: ASES, American Shoulder and Elbow Surgeons; AVN, avascular necrosis; BMI, body mass index; BPI, Brief Pain Inventory; DSA, digital subtraction angiography; IPM-CS, imipenem-cilastatin; KL, Kellgren-Lawrence; MRI, magnetic resonance imaging; PRTEE, Patient Rated Tennis Elbow Evaluation; QuickDASH, Quick Disability of the Arm, Shoulder, and Hand; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Abstract, not a published manuscript. Mixed pathology for chronic shoulder and elbow pain, though predominantly tendinopathy.
[b] Elbow (lateral epicondylitis), shoulder (rotator cuff tendinopathy), knee (patellar tendinopathy/iliotibial band syndrome), foot/ankle (plantar fasciitis, Achilles tendinopathy).

2 years post procedure (1.5 ± 0.8 vs. 0.7 ± 0.6, $P = 0.002$). Importantly, there were no significant changes in cartilage, menisci, ligaments/tendons, marrow edema, bone attrition, or total WORMS scores at 24 months.

Another open-label cohort study from South Korean evaluated TAE for "KOA" in 71 knees (41 patients) (11). The mean age was 67 years and the mean BMI 25 kg/m^2. Inclusion criteria included KL grades 1 through 4, with a VAS for pain score of more than 2 out of 10, with no response to conservative therapy for 3 months. The mean duration of pain was 73 months, although it was much longer for KL grade 4 (134 months vs. 58 months, $P < 0.001$). There was no significant difference in VAS pain severity between KL 1-3 and KL 4 at baseline (5.5 [2.2] vs. 6.3 [2.2]). The 59 KL 1-3 patients experienced a significant decrease in mean VAS pain severity as early as 1 day post procedure, and although the effect decayed with time, pain was still significantly improved in all 59 patients available at 6 months. (Improvement at 1 week vs. 6 months: 3.1 vs. 1.9; *P*-for-trend <0.01.) In contrast, although the 12 KL grade 4 knees initially showed a similar positive response, pain relief was only statistically significantly improved through the 1-month mark and was not sustained in the 9 knees that were available (75%) for 6-month evaluation (1 week vs. 1 month vs. 6 months: 4.1 [2.1] vs. 4.4 [2.1] vs. 5.9 [2.1], $P < 0.01$ at 1 week and 1 month only). In this study, only the KL 1-3 patients achieved "clinical success"—defined as at least a 50% reduction in VAS pain severity—at 3 months.

Both of these studies used imipenem-cilastatin (Merck) (IPM-CS) as the embolic agents, which is not readily available in North America.

A case series of TAE for "KOA" from Japan reported on outcomes in 33 knees (21 patients) with KL grades 1 through 3 and compared the safety and efficacy of IPM-CS with that of 100-300 microne polymer-based microsphere Embosphere (ES) (Merit Medical) (10). Whereas both groups sustained significant improvements in 3-month WOMAC pain scores (11.7 to 5 [ES] and 11.1 to 3.7 [IPM-CS], respectively, $P < 0.05$) and WOMAC total scores (41.3 to 22.2 [ES] and 41.3 to 17.3 [IPM-CS], respectively, $P < 0.05$), there was no significant difference between the two embolic agents. Neither group sustained any major adverse event.

Another case series from the United States evaluated 20 knees treated with TAE using Embozene (Varian Medical) (8). They also included KL grades 1 through 3, but the subjects had higher mean BMIs (35 kg/m^2) and a median KL grade of 3. At 6 months, there were significant improvements in mean WOMAC scores between baseline and 1-, 3-, and 6-month follow-up time points (61 ± 12, 24 ± 17, 31 ± 21, and 31 ± 6, $P < 0.0001$). The mean VAS for pain also improved (76 ± 14, 22 ± 19, 34 ± 26, and 31 ± 28, $P < 0.0001$). Although two patients had evidence of marrow edema on 1-month follow-up MRI, no major adverse events or complications resulted from the procedure.

Enthesopathy and tendinopathy. Three papers and three abstracts evaluated TAE for enthesopathy and tendinopathy. All studies reported 100% technical success without any major adverse events. Minor complications included self-resolving access site hematoma and transient cutaneous

discoloration in a minority of patients. No skin ulceration, osteonecrosis, myotendinous injury, or ligamentous injury were reported.

A small case series from Japan reported outcomes in seven patients undergoing TAE for refractory tendinopathy/enthesopathy of the elbow (lateral epicondylitis), shoulder (rotator cuff tendinopathy), knee (iliotibial band syndrome/patellar tendinopathy), and ankle (plantar fasciitis, Achilles tendinopathy) (16). Pain was refractory to conservative therapy for at least 3 months, and on entry, pain score was greater than 50 of 100 mm on a VAS scale. Mean VAS pain scores improved in seven of seven (100%) patients at 4 months (mean [SD] for baseline vs. 4 months was 72.7 [9.9] vs. 9.7 [6.8]; $P < 0.001$.)

Another small, single-center case series from South Korea evaluated the safety and efficacy of TAE for chronic shoulder and elbow pain secondary to rotator cuff tendinopathy, calcific tendinitis, and lateral and medial epicondylitis (18). This study evaluated 32 joints (19 shoulders, 13 elbows) in 24 patients all refractory to conservative therapy. Mean VAS pain scores on a 10-point scale were improved at 4 months compared with baseline (5.9 vs. 2.3; $P < 0.05$). They also investigated whether pain improvement was associated with evidence of enhancing hypervascularity on MRI. Patients with enhancement demonstrated significantly greater mean improvements in VAS pain at 4 months in comparison with those without enhancement (4.2 vs. 2.7; $P < 0.05$). Of note, only 61.5% of patients without enhancement experienced a reduction in pain during the study period, compared with 89.5% of patients with enhancement.

A case series from Japan evaluated TAE to treat pain due to lateral epicondylitis (13). Twenty-four patients (24 elbows) with a VAS pain score of more than 50 mm for longer than 6 months' duration and refractory to at least 3 months of conservative therapy were enrolled. Maximal VAS, Quick Disability of the Arm, Shoulder, and Hand (QuickDASH), and Patient Rated Tennis Elbow Evaluation (PRTEE) scores were measured. Clinical outcomes were assessed at baseline through 24 months after "embolization". Pain-free grip strength and MRI were assessed at baseline and 24 months only. Mean baseline symptom duration was 17 months (6-60 months) with a significant reduction in scores at all time intervals relative to baseline. The mean (SD) baseline and 24-month QuickDASH and VAS scores were 50.8 (14.2) versus 2.7 (2.8) and 77 (16) versus 11 (8), respectively ($P < 0.001$ for both). The mean (SD) PRTEE scores followed a similar positive trend (28.1 [8.3] vs. 3.3 [2.7], $P < 0.001$). Of treated patients, 36% required a second "embolization" procedure after 6 months to maintain symptom improvement. A subsequent abstract from Japan with 52 patients reflected the same trends and effect size (12). There was a significant improvement in pain-free grip strength as well as MRI criteria at 24 months, with a significant reduction in tendinosis/tear scores and no evidence of osteonecrosis, myotendinous, cartilaginous, or ligamentous injury on imaging.

Adhesive capsulitis. One study from Japan evaluated TAE for treatment of adhesive capsulitis in 25 patients (25 shoulders) (15). Adhesive capsulitis was defined as nighttime shoulder pain, painful restriction of passive and active forward elevation of less than 100 degrees, painful restriction of external rotation to less than 50% of the contralateral side, and normal radiographs. All patients were refractory to conservative therapy for at least 3 months and had moderate to severe pain (VAS score of more than 50 mm). Patients with malignancy, full-thickness rotator cuff tears, prior shoulder surgery, and those who were felt to be starting to improve were excluded. There was a 100% technical success rate without major complication. Minor complications included transient periprocedural pain, self-resolving radial artery vasospasm, and transient fever, all in a small minority of treated patients. No shoulder instability, weakness, paresthesia, osteonecrosis, or skin ulceration was reported. There were significant improvements in mean nighttime pain scores (68 [14] vs. 2 [5]) and overall VAS pain scores (82 [11] vs. 5 [11]), respectively ($P < 0.001$ for both), in the 24 of 25 (96%) of subjects evaluated at 6 months. In addition, range of motion also significant improved. Mean (SD) American Shoulder and Elbow Surgeons (ASES) scores also reflected functional improvements at 6 months (16.1 [3.6] vs. 96.6 [4.3], $P < 0.001$).

Chronic myalgia. A single small case series of 10 patients from Japan explored the use of TAE for the management of chronic trapezius myalgia. All patients had pain of greater than 1-year duration, and those with cervical radiculopathy, cervical stenosis, and facet arthritis were excluded (14). Mean symptom duration was 7.1 years. No major or minor complications were reported. Brief Pain Inventory intensity and interference scores significantly improved at 6 months (8.8 [1.3] vs. 5.8 [3.5] and 5.2 [1.4] vs. 3.6 [3.0], respectively, $P < 0.01$ for both metrics).

DISCUSSION

Chronic "musculoskeletal pain" is a major public health burden, and identifying a safe, effective, and durable intervention would have multiple benefits. Effective pain control would lead to major improvements in quality of life, and improved mobility could lead to decreased morbidity and mortality (22). Because they are relatively inexpensive and nonaddictive and have proven efficacy, NSAIDs are the current mainstay of pharmacologic therapy formats musculoskeletal disorders (23,24). However, this effective pain relief comes with considerable risk. The Food and Drug Administration recently strengthened an existing label warning that NSAIDs increase the chance of a heart attack or stroke (25). Gastrointestinal adverse events are also a considerable risk (26). COX-2 inhibitors, initially heralded as safer alternatives, have been shown to have similar cardiovascular risks as most other NSAIDs (26). Although alternate therapies such as opioids are effective, the risks of habituation and addiction make them very poor

choices for chronic pain (27). In patients with "KOA", repeated intra-articular corticosteroid injections have been shown to cause thinning of the cartilage, decreasing enthusiasm for using this local anti-inflammatory therapy chronically (28). It is unclear whether intraarticular therapies such as hyaluronan, platelet rich plasma, or stem cell therapy provide any benefit beyond a placebo effect (29–31). For tendinopathy, which can be challenging to treat, there is some evidence that NSAID use may even interfere with the healing process (32). A procedure such as TAE—which leads to involution of the inflammatory tissue, which is the nociceptive stimulus, and would thus potentially prevent the need for ongoing therapy—is particularly appealing.

Although OA was once considered a non-inflammatory "wear and tear" arthritis, it is now well proven that synovitis is common in OA, and this pathogenically inflamed synovium is characterized by angiogenesis (33). The proliferation of abnormal vessels promotes the increased migration of immune effector cells to the area, which lead to both cartilage destruction and perpetuation of local inflammation (34). There are active lines of investigation to develop interventions to medically block pro-angiogenic pathways in OA (33). TAE similarly targets hypervascular synovium, but physically rather than medically debulking the pathogenic synovium. While the biology of tendinopathy is less well studied, macrophages, chronic inflammation, and angiogenesis are all thought to play crucial roles in propagating inflammation (35,36).

Neurogenesis can be up-regulated in parallel with angiogenesis, which can also contribute to the development and maintenance of chronic pain (37–39). The role that angiogenesis plays in the etiology of both OA and tendinopathy makes both of these conditions particularly amenable to the targeting of hypervascular tissue by TAE, and data suggest that TAE efficacy is associated with degree of neoangiogenesis (18). Whether TAE may favorably modulate the inflammatory process at the local level requires further study.

These results suggest that TAE is effective in the treatment of chronically painful musculoskeletal conditions and that results are durable up to 24 months. These data also suggest that there are certain predictors of poor response to TAE, such as KL 4 in "KOA", high BMI, and lack of evidence of angiogenesis on imaging (9,11,18). It is particularly encouraging that very few complications were reported, none of which were severe. There were no cases of osteonecrosis, ligamentous, cartilaginous, or myotendinous injury. Given the technical challenges of TAE in comparison to more conventional procedures such as steroid injection, multicenter trials with multiple operators of variable experience are needed to determine whether similar excellent results are achievable outside expert centers. This is important, as ischemia of the normal articular and peri-articular tissues from nontarget "embolization" is a known risk factor of embolic procedures (8).

TAE may be particularly appealing in the treatment of "KOA". Synovitis is seen in over 50% of painful "KOA" cases and has been shown to correlate with severity of OA pain in cross-sectional studies, and changes in synovitis correlate with changes in pain severity longitudinally (40–42). This suggests that targeting local areas of synovitis with TAE may be an effective method of improving "KOA" pain. This has important public health implications. It is estimated that almost *half* of US adults will develop "KOA" by age 85 (43). These already high rates are likely to increase substantially over the coming decades owing to rising obesity rates, the aging population, and knee injuries (44–46). Unfortunately, many patients with "KOA" are unable to obtain adequate pain relief from standard pharmacologic therapies or are not able to take these medications safely because of age or comorbidities. Further research is also needed to see whether TAE could decrease the need for knee replacements because, without viable alternatives, it is projected that half of all US adults currently diagnosed with "KOA" will eventually undergo a total knee replacement (TKR) (47). Although it is expensive, if TAE could decrease the use of other therapies, minimize their associated complications, or delay or defer TKR, it may prove cost-effective.

TAE may also provide a reasonable surgical alternative for the management of chronic symptomatic tendinopathy/enthesopathy. Abnormal neovascularization and accompanying neurogenesis at the site of tendinosis has been implicated in painful tendinopathy, and a double-blind randomized control trial demonstrated symptomatic improvement after direct percutaneous injection of a sclerosant into areas of abnormal neovascularity (48). The association between paratendinous inflammation, angiogenesis, and nociceptive mediators is worth further inquiry (49). Interestingly, on follow-up MRI of lateral epicondylitis after TAE, there was resolution of tendinosis on imaging, suggesting that TAE may modulate the remodeling process within the tendon (12,13). Additionally, although experimental models suggest that targeting angiogenesis may accelerate tendon healing in tendinopathy, the appropriate time course for intervention is not clear (50).

However, despite these encouraging findings, this review points out important research gaps. All published data are derived from open-label case series or cohort studies, which are at risk of selection bias as well as the placebo effect owing to lack of a control group. The heterogeneity of subjects, conditions, and outcome measures precluded a quantitative synthesis of these results. These studies are too small to identify common or severe adverse events. Most of these studies were performed in a limited number of centers with homogenous populations, and results may not be generalizable. For example, the mean BMI in the largest study of "KOA" was 25 kg/m^2, much lower than the average BMI of patients with "KOA" in North America and Europe. Furthermore, many of these conditions improve on their own, and regression to the mean cannot be excluded. There are also very little data on differences between embolic agents used in TAE. In theory, agents that are not permanent, such as IPM-CS, may be less likely to cause adverse events, but this has not yet been

shown. Similarly, animal studies suggest that an embolic product with a hydrogel core and a Polyzene-F shell may have variable deformation in tissue compared with tris-acryl gelatin microspheres. This may make the level of vascular occlusion more unpredictable when using the former product; however, again, this has not been shown in human studies.

In order to determine whether TAE is an effective treatment for chronic musculoskeletal conditions, prospective randomized trials with control interventions are desperately needed, and a number are reported to be underway (NCT03460665) (51). Although randomized controlled trials of procedures are notoriously challenging, there are guidelines to ensure trial quality, reproducibility, and generalizability (52). If TAE proves to be as effective and safe as suggested by these early studies, it may have an important role in the treatment of chronic "musculoskeletal pain".

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AUTHOR CONTRIBUTIONS

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