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REVIEW

# Current Status of Trans-Arterial Embolization in Pain Management of Musculoskeletal Inflammatory Conditions — An Evidence-Based Review

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**Abstract**
*Objective* To summarize the literature on trans-arterial embolization in inflammatory musculoskeletal conditions, focusing on efficacy and safety.
*Materials and Methods* PRISMA guidelines were followed. A systematic literature search revealed 19 studies, with a total of 394 participants, eligible for inclusion.
*Results* The included studies consisted of case reports/series and non-randomized interventional studies, with knee osteoarthritis and adhesive capsulitis of the shoulder as the most frequent conditions. In all studies except one, pain was reduced up to four years after treatment. All adverse events were transient. Due to high heterogeneity, meta-analysis was not possible.
*Conclusion* The included early studies showed encouraging results regarding efficacy and safety. However, randomized, placebo-controlled trials are warranted.

**Keywords** Interventional radiology · Inflammatory musculoskeletal disorders · Trans-arterial embolization · Pain management

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## Introduction

Trans-arterial embolization (TAE) is an established minimal invasive procedure for a wide variety of conditions [1–3]. Inflammation stimulates angiogenesis in a positive feedback mechanism and promotes sensitization and growth of sensory nerves [4, 5]. This makes TAE of angiogenetic neovessels a possible target for the treatment of pain in inflammatory diseases.

The first study, of TAE as a potential pain management of inflammatory musculoskeletal diseases, was published in 2013 on tendinopathies and enthesopathies [6]. Since then, this and other research groups have published studies on various inflammatory musculoskeletal conditions, predominately knee osteoarthritis (OA), and adhesive capsulitis [7].

In this systematic review, we reported and evaluated the available research on TAE of inflammatory musculoskeletal conditions. The aim was to investigate the efficacy, safety, and current evidence, and to provide suggestions for future directions.

## Materials and Methods

This systematic review was conducted in accordance to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [8] and a pre-specified research protocol. This systematic review did not include any material that necessitated ethics committee or institutional review board approval.

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### Information Sources and Search Strategy

A systematic search was performed in MEDLINE (via PubMed), EMBASE (via Ovid), Web of Science, BIOSIS, and Cochrane Library. The search was built with following MeSH terms: "embolization, therapeutic," "pain," and "musculoskeletal diseases" as well as free text search with relevant synonyms. For the EMBASE search, corresponding subject headings were used: "artificial embolization," "pain," and "musculoskeletal system inflammation." The full search strategy is available as Online Resource. Covidence Systematic Review software [9] was used to remove duplicates. The initial search was conducted on January 20, 2021, and email alerts were set up to provide weekly updates. A final search was run on February 26, 2021. Reference lists were searched, and PubMed's and Google Scholar's "related articles search" was performed on all included articles and relevant reviews to identify additional studies. The search was developed and conducted by first author LH and reviewed and approved by all co-authors as well as two librarians from the University of Copenhagen experienced in scientific literature search.

### Eligibility Criteria and Study Selection

Studies regarding TAE as pain treatment of inflammatory musculoskeletal conditions in humans were eligible for inclusion. We included case reports, randomized clinical trials, and non-randomized retro- and prospective interventional studies. Reviews, abstracts, supplements, and conference papers were excluded. No time or language restrictions were applied, but only studies in peer-reviewed journals were included.

Two authors (LH and MT) independently conducted abstract and full-text screening as well as subsequent pilot tested data extraction of included articles using Covidence Systematic Review software [9]. Disagreements were resolved by discussion and final consensus.

### Outcome Measures

The primary outcome measure was pain reduction, after TAE of inflammatory musculoskeletal diseases, reported by visual analogue scale (VAS) 0–100 mm [10] or comparable rating systems. Secondary outcomes were reduction in oral analgesics, reported as percentage of participants taking paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and/or opioids, and the incidence and grade of complications using the Society of Interventional Radiology (SIR) Standards of Practice Committee adverse event classification [11].

### Study Quality

We used the methodological index for non-randomized studies (MINORS) tool for evaluating the quality of the included studies [12]. The evaluation was done independently by two authors (LH and MT), and disagreements were resolved by consensus. Robvis online visualization tool was used to graphically present the risk of bias data [13]. Case reports were not scored since risk of bias is critical under all circumstances in these domains. Moreover, we used Oxford Centre for Evidence-Based Medicine 2011 guidelines to grade the levels of evidence in a 1–5 scale [14].

### Statistical Considerations

A meta-analysis was not possible due to large clinical heterogeneity, inconsistent outcome measures, and highly biased study types. In studies, reporting VAS 0–10 cm or equivalent pain scales (Numeric Rating Scale 0–10 [15], Brief Pain Inventory 0–10 [16]), conversion was made to VAS 0–100 mm for better comparison between studies. A $p$ value $< 0.05$ was considered statistically significant.

## Results

### Study Selection

The final database search returned 993 references after duplicates were removed. Searching of references and related articles resulted in one additional record included in the screening process. After abstract and full-text screening, 19 studies fulfilled eligibility criteria and were included in this qualitative systematic review: eighteen studies in English and one in German. Figure 1 illustrates the study selection process using a PRISMA flowchart [8].

### Study Characteristics

The included studies were either case reports/series or prospective/retrospective interventional studies without randomization or comparison groups. The 19 included studies consisted of a total of 394 participants, age range 24–87 years, 66% females. Since 85 participants received TAE either bilateral or for two separate conditions, the total number of embolization procedures was 479. The included studies represented a variety of different inflammatory musculoskeletal diseases presented in Table 1 and Fig. 2. The final diagnosis was corroborated by both clinical and radiological criteria in all studies, except Okuno et al. [6] and Iwamoto et al. [17], who did not mention radiological examinations. Body mass index (BMI) was

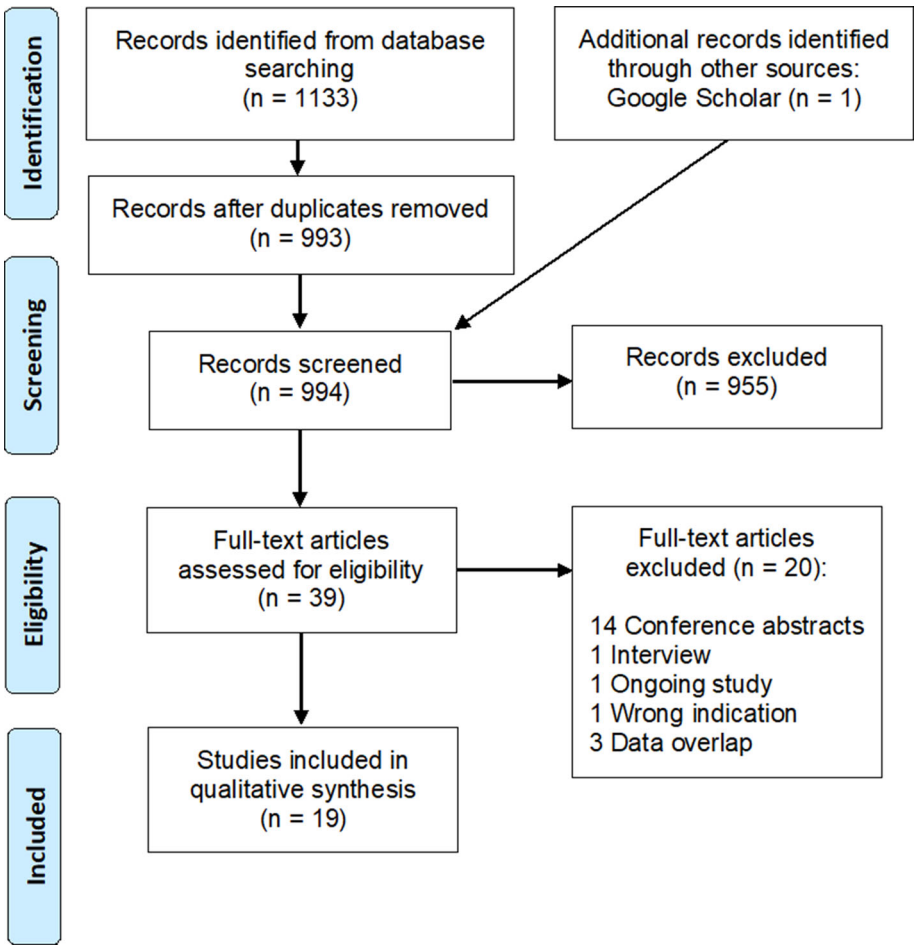


**Fig. 1** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

reported only in studies concerning knee OA, and the mean/median was lower in studies conducted in Asia ([18]: 25 kg/m$^2$ (range19–41); [19]: 25 ± 4 kg/m$^2$; [20]: 26 kg/m$^2$ (range 22–33)) than in USA ([21]: 34 kg/m$^2$ (range 22–51)), Australia ([22]: 31 kg/m$^2$ (range 25–50)), and UK ([23]: 30 kg/m$^2$ (range 20–48)).

Two studies performed TAE in a combination of mild sedation and local anesthesia [21, 22], two did not comment on this [20, 23], and the remaining studies only used local anesthesia. Different embolic agents were used, including the resorbable embolic agent (Imipenem/Cilastatin) and/or permanent embolic agents (polyvinyl alcohol particles, gelatin sponge particles, or calibrated microspheres). The number of arteries embolized during one TAE procedure varied from 1 to 7. Mean procedure time was reported by Fernández et al. [24] as 48 ± 17 min for adhesive capsulitis, and by Bagla et al. [21] as 81 ± 31 min with a mean fluoroscopy duration of 29 ± 12 min and reference air kerma of 128 ± 106 mGy for knee OA. Little et al. [23] reported a mean fluoroscopy duration of 14 ± 10 min and reference air kerma of 96 ± 75 mGy for knee OA.

In four studies, participants with inadequate pain response after initial TAE were offered re-embolization [17, 18, 22, 24]. Seven studies reported one to four participants lost to follow-up [17–19, 21–23, 25], primarily due to exclusion based on continuous pain and an offer of surgery with total knee arthroplasty (TKA). Follow-up time and range are shown in Table 1.

Prior to TAE, all studies performed angiography, looking for abnormal neovessels, described as hyperemic areas, identified by "tumor-blush"-type enhancement often accompanied early venous drainage. These signs were found in 100% of participants in 12 of the included studies. In the remaining studies [17, 24, 26–29], except Little et al. [23], participants were embolized despite the absence of abnormal vessels. The phenomenon "evoked pain," including pain, itching, or heat sensation during contrast injection, was used to identify arteries responsible for the participants usual area of pain.

## Outcome Measures

The primary outcome, pain reduction, was reported quantitatively or qualitatively in all included studies. Most

**Table 1** Characteristics of included studies

| Study | Year | Country | Study design | Condition | TAE, (bilat.) | Females, % | Age, mean | Embolic agents | Follow-up, months |
|---|---|---|---|---|---|---|---|---|---|
| Okuno [6] | 2013 | Japan | Prospective | Tendinopathy or enthesopathy[a] | 7 | 29 | 52 | IPM/CS[d] | 4 |
| Okuno [25] | 2017 | Japan | Prospective | Adhesive capsulitis | 25 | 68 | 54 | IPM/CS[d] | 30–44 (mean 36) |
| Okuno [18] | 2017 | Japan | Prospective | Knee OA (KL 1–3) | 72 (23) | 68 | 64 | IPM/CS[d] or calibrated particles[e] | 6–48 |
| Iwamoto [17] | 2017 | Japan | Prospective | Lateral epicondylitis | 24 | 42 | 52 | IPM/CS[d] ± calibrated particles[e,f] | 24 |
| Hwang [35] | 2018 | Korea | Retrospective | Tendinopathy[b] | 13 (2) | 77 | 52 | IPM/CS[g] or calibrated particles[f] | 4 |
| Lee [19] | 2019 | Korea | Retrospective | Knee OA (KL 1–4) | 41 (30) | 76 | 67 | IPM/CS[g] | 6–19 (mean 10) |
| Shibuya [26] | 2019 | Japan | Case report | Phantom limb pain | 1 | 0 | 46* | IPM/CS[d] | 6 |
| Ciampi [36] | 2020 | Spain | Prospective | Adhesive capsulitis | 9 | 67 | 47* | IPM/CS[h] | 6 |
| Katoh [30] | 2020 | Germany | Case series | Shoulder OA or tendinopathy[c] | 3 | 33 | 52 | IPM/CS[i] | 3 |
| Correa [28] | 2020 | Brazil | Case report | Hip synovitis | 1 | 100 | 77* | PVA particles[j] | 4 |
| Bagla [21] | 2020 | USA | Prospective | Knee OA (KL 1–3) | 20 | 55 | 63* | Calibrated particles[e] | 6 |
| Landers [22] | 2020 | Australia | Prospective | Knee OA (KL 1–2) | 10 | 40 | 62* | IPM/CS[d] or PVA particles | 12–24 (mean 22) |
| Choi [20] | 2020 | Korea | Retrospective | Knee OA (KL 1–4) | 18 (10) | 78 | 69 | IPM/CS + gelatin sponge particles | 3 |
| Lauko [34] | 2020 | USA | Case report | Knee OA (KL 3) | 1 | 100 | 64* | Calibrated particles[e] | 6 |
| Chau [31] | 2020 | France | Prospective | Knee pain (former TKA) | 4 | 50 | 73 | Calibrated particles[e] | 1 |
| Fernandez [24] | 2021 | Spain | Prospective | Adhesive capsulitis | 40 | 88 | 50 | IPM/CS[h] | 12–48 (mean 21) |
| Fernandez [29] | 2021 | Spain | Prospective | Secondary stiff shoulder | 25 | 80 | 49* | IPM/CS[h] | 6 |
| Shibuya [27] | 2021 | Japan | Prospective | Trapezius myalgia | 42 (20) | 62 | 56 | IPM/CS[d] | 6 |
| Little [23] | 2021 | UK | Prospective | Knee OA (KL 1–3) | 38 | 53 | 60* | Calibrated particles[f] | 3–12 (mean 8) |

[*] Median

[a] Patellar tendinopathy, $n = 1$; rotator cuff tendinopathy, $n = 2$; plantar fasciitis, $n = 1$; lateral epicondylitis, $n = 1$; iliotibial band syndrome, $n = 1$; Achilles insertion tendinopathy, n = 1

[b] Lateral epicondylitis, $n = 7$; rotator cuff tendinopathy, $n = 6$; calcific tendinitis, n = 2

[c] Shoulder OA, $n = 1$; medial epicondylitis, $n = 1$; patellar tendinopathy, $n = 1$

Manufactures: [d] Primaxin, Merck, Whitehouse Station, New Jersey, USA. [e] Embozene, Boston Scientific, Marlborough, MA, USA. [f] Embosphere, Merit Medical, South Jordan, UT, USA. [g] Prepenum, JW Pharmaceutical, Seoul, Korea. [h] Aurovitsas, Spain. [i] Fresenius-KABI, Singapore. [j] BeadBlock microspheres, BTG, Farnham, UK

*IPM/CS*, Imipenem/Cilastatin; *KL*, Kellgren–Lawrence grade; *OA*, osteoarthritis; *PVA*, polyvinyl alcohol; *TAE,* trans-arterial embolization; *TKA*, total knee arthroplasty

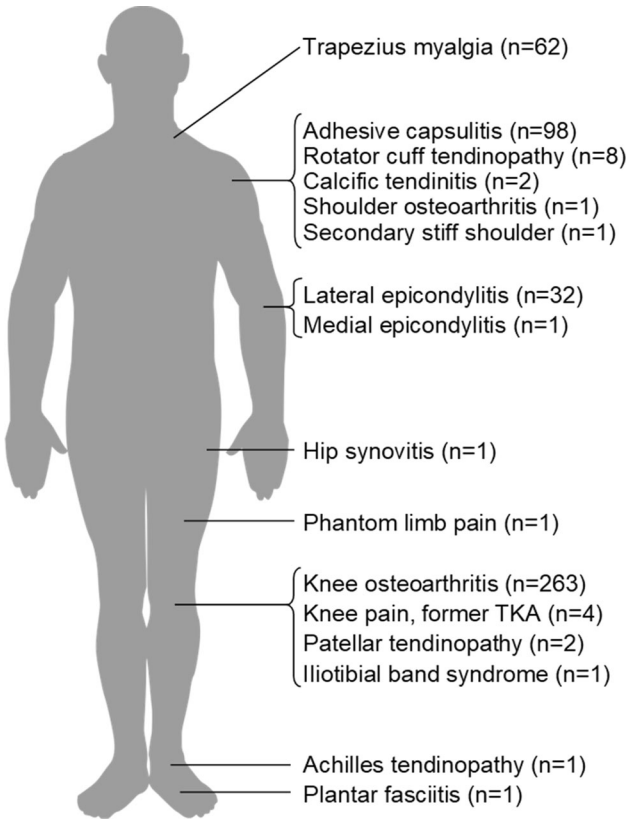


**Fig. 2** Inflammatory musculoskeletal conditions embolized in included studies. Number of total cases in brackets. *Abbreviation*: *TKA*, total knee arthroplasty

studies used a minimum, but varying, pain score as inclusion criterion, and reported pain heterogeneously as worst/least/mean/daytime/nighttime/during activity or unspecified. Figure 3 illustrates pain development after TAE in studies reporting VAS or comparative rating scales. The four case reports/series showed a marked decline in pain post-treatment [26, 28, 30, 31]. The remaining studies, except one [19], reported significant pain reduction at all follow-up points. Lee et al. [19] separately reported pain in groups with mild-moderate (Kellgren–Lawrence grade 1–3 [32]) versus severe knee OA (Kellgren–Lawrence grade 4). In participants with severe knee OA, pain was reduced the first month post-treatment but deteriorated thereafter.

Landers et al. [22] did not report VAS, but used the Knee Injury and Osteoarthritis Outcome Score (KOOS [33]) including a pain sub score. They found beneficial treatment effects on knee OA in the first 12 months but less apparent efficacy at two years follow-up despite repeat TAE in six participants. Choi et al. [20] reported a baseline VAS 84 ± 16, with > 30% reduction in VAS in 57% of knee OA participants after one month and in 25% after three months. Lauko et al. [34] descriptively reported that the knee OA case had severe pain pre-treatment and no pain complaints six months post-treatment.

Use of oral analgesics (including paracetamol, NSAIDs, and/or opioids) was reported by all studies except Correa et al. [28]. In the study of Choi et al. [20], the use of analgesics was, per protocol, left unchanged post-treatment. Little et al. [23] reported almost no change in the use of analgesics at final follow-up. Landers et al. [22] reported a reduction from 20 to 0% of participants using NSAIDs, while the use of paracetamol was unchanged. In the study by Lee et al. [19], the use of NSAIDs decreased in participants with mild-moderate knee OA. For participants with severe knee OA, the use initially decreased but showed a tendency to increase at 12 months (att. only 3 out of initial 12 participants were included at 12 months follow-up). In the remaining 14 studies, more than 50% of initial users had stopped taking oral analgesics at final follow-up.

Adverse events due to TAE were reported by all studies, except Correa et al. [28], and the individual and total incidences are listed in Table 2. Bagla et al. [21] reported two cases of plantar numbness of the great toe, which was the only complication classified as major. The participants were treated with gabapentin, and the symptoms resolved within 2 weeks. The research group decided to increase the embolic particle size from 75 to 100 µm (Embozene, Boston Scientific, Marlborough, MA, USA), and thereafter, no further post-procedural neurologic changes were seen. Great toe paresthesia and the most common adverse event, skin discoloration, presumably occurred due to non-target embolization. Little et al. [23] and Fernández et al. [29] used cooling strategies such as topical ice packs to promote temporary vasoconstriction, minimizing non-target embolization of cutaneous arterial branches. In four studies, the participants were per protocol hospitalized until one day after TAE to observe for adverse events [20, 30, 35, 36]. In the remaining studies, the participants were discharged on the day of TAE. All adverse events were transient, and no participants were hospitalized or experienced sequelae at end follow-up.

Physical tests were performed in six studies, with five studies reporting significant improvements [17, 24, 25, 29, 36], and one study reporting substantial improvement but no $p$ value [22].

Magnetic resonance imaging (MRI) was performed pre- and post-intervention in six studies [17, 18, 21–23, 28]. Follow-up time, MRI sequences, and outcome parameters were very heterogenic and evidence sparse, but inflammatory parameters were reported to decrease after TAE.

A variety of embolic agents were used including permanent and non-permanent materials. Due to the heterogeneity and lack of randomization in the material, we did not find it appropriate to compare the efficacy and safety of these agents.

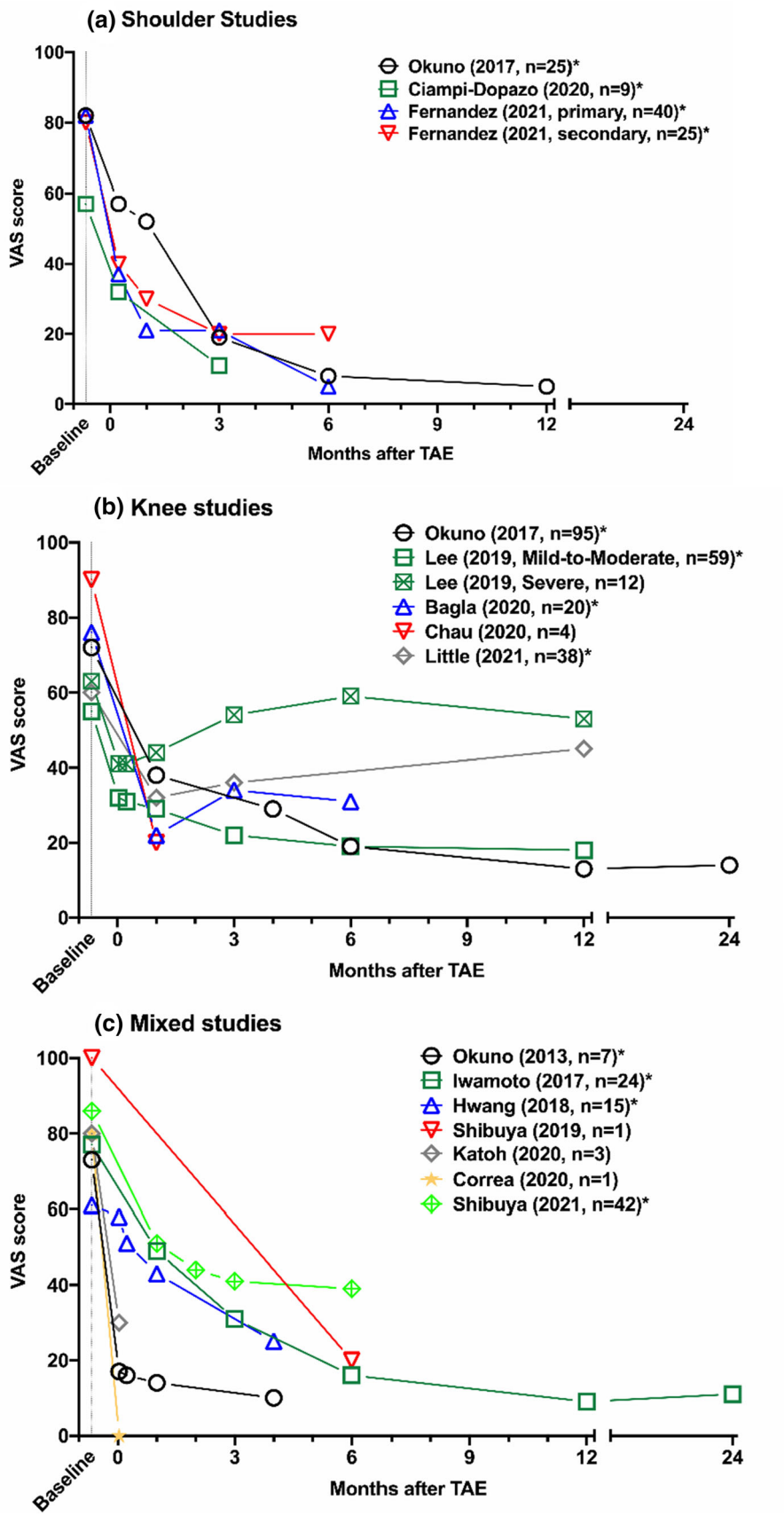


**Fig. 3** Pain development after TAE in studies reporting VAS or comparable rating scores **a** shoulder studies; **b** knee studies; **c** mixed studies. *Significant reduction of VAS score at all follow-up points. n = number of embolized conditions, including bilateral cases, except Shibuya et al. (2021), where bilateral embolized participants only reported an overall pain score. *Abbreviations*: *TAE*, trans-arterial embolization; *VAS*, visual analogue scale

**Table 2** Summary of reported adverse events in included studies

| Study | Minor[a] adverse events, n (%) | | | | Major[a] adverse events, n (%) | No adverse events |
|---|---|---|---|---|---|---|
| | Skin discoloration | Access site hematoma | Post-procedural pain | Transient fever | | |
| Okuno [6] | – | 1 (14%) | – | – | – | – |
| Okuno [25] | – | – | 1 (4%) | 1 (4%) | – | – |
| Okuno [18] | 4 (6%) | 12 (17%) | – | – | – | – |
| Iwamoto [17] | – | – | – | – | – | × |
| Hwang [35] | 1 (8%) | – | – | – | – | – |
| Lee [19] | 4 (10%) | 5 (12%) | – | 1 (2%) | – | – |
| Shibuya [26] | – | – | – | – | – | – |
| Ciampi [36] | – | – | – | – | – | – |
| Katoh [30] | 1 (33%) | – | – | – | – | – |
| Bagla [21] | 13 (65%) | 1 (5%) | – | – | 2[b] (10%) | – |
| Landers [22] | – | 1 (10%) | – | – | – | – |
| Choi [20] | 4 (22%) | – | 3 (17%) | – | – | – |
| Lauko [34] | 1 (100%) | – | – | – | – | – |
| Chau [31] | – | – | 1 (25%) | – | – | – |
| Fernandez [24] | – | 2 (5%) | – | – | – | – |
| Fernandez [29] | 4 (16%) | – | – | – | – | – |
| Shibuya [27] | – | 1 (2%) | – | – | – | – |
| Little [23] | 4 (11%) | 1 (3%) | – | – | – | – |
| **All above, (393 participants)** | **36 (9%)** | **24 (6%)** | **5 (1%)** | **2 (< 1%)** | **2 (< 1%)** | – |

[a] Based on the Society of Interventional Radiology (SIR) Standards of Practice Committee adverse event classification

[b] Transient plantar numbness of the great toe

*n* = number and % = percentage of participants with the adverse event (bilateral cases not counted twice)

*TAE*, trans-arterial embolization

## Study Quality

Quality assessment using the MINORS criteria [12] is visualized graphically as "traffic-light" and weighted bar plots in Fig. 4, using the Robvis online visualization tool [13]. Case reports/series [26, 28, 30, 34] were not included since the risk of bias per default is critical. None of the included studies compared TAE to a sham/placebo-intervention or other control groups. In addition, several studies (Fig. 4, D2) did not describe the inclusion of consecutive participants, leading to high risk of selection bias. Since all studies focused on pain, which is highly subjective and based on participant porting, a high risk of response bias was present. TAE, for inflammatory musculoskeletal disease, is a new treatment option, which imply an inherent risk of publication bias in favor of positive outcome results. This systematic review contained high biased and very heterogenic studies. Given this, a quantitative meta-analysis was not appropriate. Regarding the Oxford Centre for Evidence-Based Medicine 2011 guidelines [14], the individual non-randomized follow-up studies represented level 3 evidence and case series level 4. This systematic review including level > 2 studies was graded as level 2 evidence.

## Discussion

A systematic literature search, for current scientific knowledge on TAE of inflammatory musculoskeletal conditions, included only low evidence research as case reports/series or non-randomized, unblinded, interventional studies. In all studies, but one [19], pain was reduced up to four years after TAE. In most of the included studies, oral analgesics were reduced with more than 50% at final follow-up. All adverse events were transient, and no sequelae were reported. Due to study heterogeneity, a meta-analysis was not an option.

Knee OA and adhesive capsulitis were the most frequently studied conditions, but as presented, TAE has

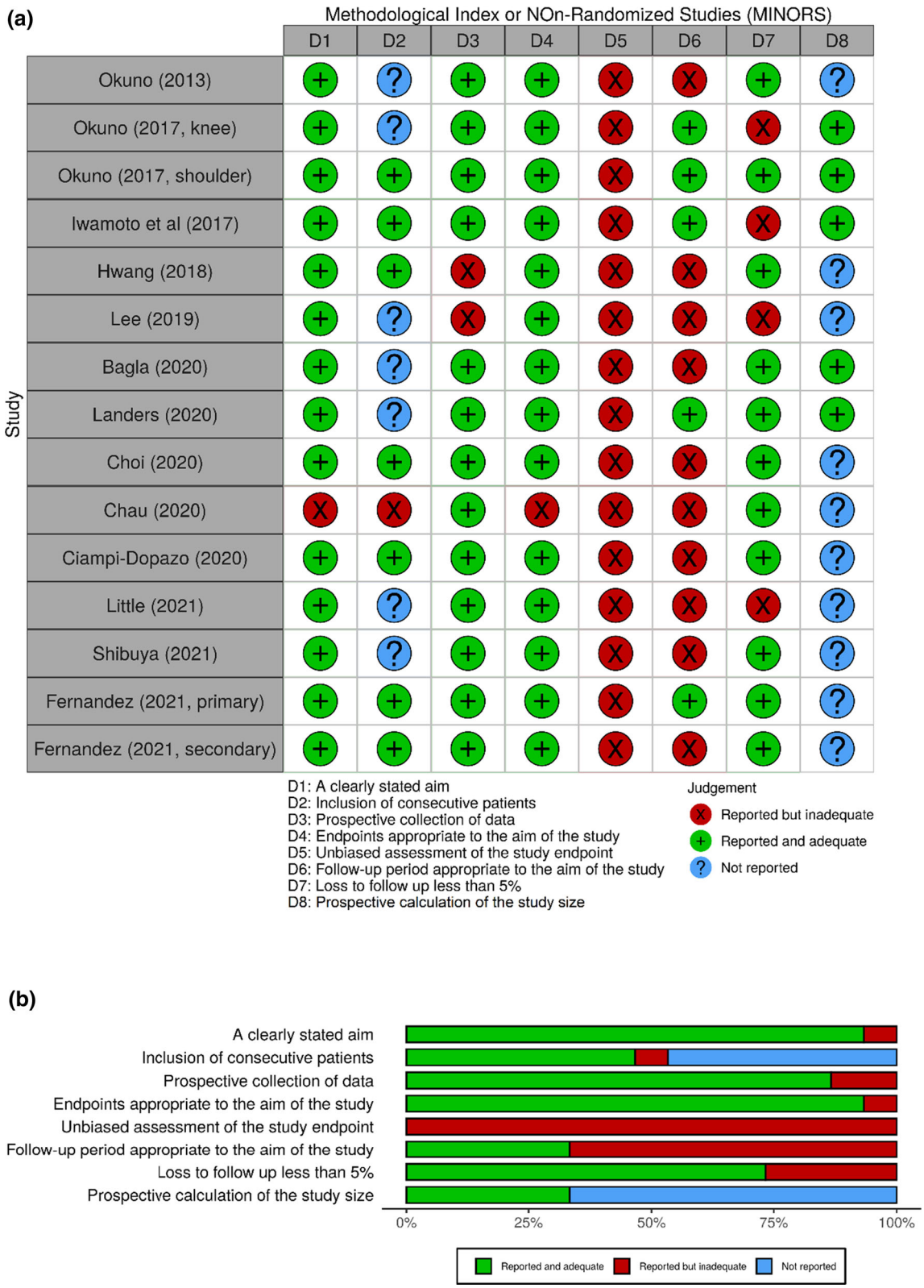


**Fig. 4** Quality assessment of included studies **a** "traffic-light" plot; **b** weighted bar plot. Methodological index for non-randomized studies (MINORS) tool was used

already been investigated in several inflammatory musculoskeletal conditions, despite the low evidence and lack of randomized controlled trials. TAE is not a curative treatment in chronic disorders like OA but a possible pain management for a yet unknown post-interventional period. Moreover, inflammatory musculoskeletal disorders are benign, and therefore, adverse events must be minor and transient to be justified. This systematic review showed promising technical results with only two adverse events classified as major, which were transient and possible avoidable.

Regional pain, the main outcome in most of the existing research, is a highly subjective effect measure and bias must be considered, especially in unblinded studies. Inflammatory pain is a challenge to measure in clinical trials since it fluctuates, is day- and activity dependent, and of multifaceted nature. This is reflected in the included studies, where pain is reported inconsistently and unspecific. Lee et al. [19] did, as the only study, not find a pain reduction after TAE. This was based on limited data on participants with severe knee OA, and the evidence was insufficient to rule out the potential of TAE in this patient group.

Use of analgesics and changes in physical activity are surrogate measurements and possible confounders of pain, and the measurements influence pain as well as each other internally. However, in most of the included studies a reduction in analgesics and improvement in physical activity was noted, which favors the potential role of TAE as pain treatment.

### Limitations

This systematic review was limited by heterogeneity in population, evaluated interventions, and outcome measurements of included studies. Quantitative, statistical analyses, including meta-analysis, were not deemed possible and a qualitative approach was selected. In addition, the included studies were generally small and suffered from significant risk of bias. Moreover, this review does not include a comparator as none of the studies are controlled randomized or non-randomized studies.

### Future Directions

Randomized placebo-controlled clinical trials are warranted, to clarify efficacy and to compare different embolization techniques and materials. Complete blinding of invasive procedures is difficult, but sham studies should be considered. When reporting the fluctuating outcome, regional pain, a clear definition, continuous follow-up periods, and reporting of confounders as analgesic use and activity level are important. Moreover, inclusion of objective effect measures, as imaging, is highly recommended. Clinical relevance must be considered, when deciding on follow-up length and adjusted due to the condition studied. Longer follow-up periods are warranted to conclude the long-term efficacy of chronic conditions as osteoarthritis. In temporary inflammatory conditions, including adhesive shoulder capsulitis, short- and midterm efficacy is important in the evaluation of clinical relevance.

## Conclusion

The included studies showed promising results regarding efficacy and safety of TAE. However, the evidence is very low and randomized clinical trials with sham interventions are needed, to clarify the role of TAE in pain management of inflammatory musculoskeletal conditions.

**Author Contributions** All authors contributed to the study conception and design. The literature search was developed and conducted by first author LH and reviewed and approved by all co-authors. Screening of eligible studies and data extraction were done independently by LH and MT. The first draft of the manuscript was written by LH with supervision by MT and LL. All authors reviewed, edited, and approved the final manuscript.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent** For this type of study, informed consent is not required.

**Consent for Publication** For this type of study, consent for publication is not required.

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