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Genicular artery embolization for early-stage knee osteoarthritis: results from a triple-blind single-centre randomized controlled trial

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Aims

This study investigated the effects of transcatheter arterial embolization (TAE) on pain, function, and quality of life in people with early-stage symptomatic knee osteoarthritis (OA) compared to a sham procedure.

Methods

A total of 59 participants with symptomatic Kellgren-Lawrence grade 2 knee OA were randomly allocated to TAE or a sham procedure. The intervention group underwent TAE of one or more genicular arteries. The control group received a blinded sham procedure. The primary outcome was knee pain at 12 months according to the Knee injury and Osteoarthritis Outcome Score (KOOS) pain scale. Secondary outcomes included self-reported function and quality of life (KOOS, EuroQol five-dimension five-level questionnaire (EQ-5D-5L)), self-reported Global Change, six-minute walk test, 30-second chair stand test, and adverse events. Subgroup analyses compared participants who received complete embolization of all genicular arteries (as distinct from embolization of some arteries) (n = 17) with the control group (n = 29) for KOOS and Global Change scores at 12 months. Continuous variables were analyzed with quantile regression, adjusting for baseline scores. Dichotomized variables were analyzed with chi-squared tests.

Results

Overall, 58 participants provided questionnaire data at 12 months. No significant differences were found for the primary and secondary outcomes, with both groups improving following the procedure. At 12 months, KOOS pain scores improved by 41.3% and 29.4% in the intervention and control groups, respectively. No adverse events occurred. Subgroup analysis indicated that the complete embolization group had significantly better KOOS Sports and Recreation, KOOS Quality of Life, and Global Change scores than the control group; 76.5% of participants who received complete embolization reporting being moderately or much better compared to 37.9% of the control group.

Conclusion

TAE might produce benefits above placebo, but only when complete embolization of all genicular arteries is performed. Further comparative studies are required before definitive conclusions regarding the effectiveness of TAE can be made.

Level of evidence: I

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Introduction

Transcatheter arterial embolization (TAE) has emerged over the last ten years as a promising treatment option for people with recalcitrant musculoskeletal conditions such as osteoarthritis (OA), tendinopathy, and fasciopathy.[1-3] TAE introduces tiny embolic particles via an intra-arterial catheter into neovessels surrounding the painful area, thereby reducing blood flow. The primary rationale for the procedure is that chronic musculoskeletal conditions involve proliferation of neovessels into the surrounding tissues and these vessels create a hypervascular state that sustains inflammation and pain.[1] TAE aims to return the microvascular environment towards its normal state and is proposed to disrupt inflammatory processes, symptoms, and disease progression.[4]

Five TAE studies in people with knee OA have demonstrated improvements in pain and function following the procedure.[1-5] These studies used single-arm designs, which cannot account for non-specific effects. Consequently, the efficacy of TAE remains unknown, and randomized, placebo-controlled trials are required.[6] The aim of the current study was to investigate the effects of TAE on pain, function, and quality of life when compared to a sham procedure in people with early-stage symptomatic knee OA.

Methods

Study design. The study was a single-centre, parallel-arm, triple-blinded (participant, assessor, statistician), randomized controlled superiority trial with 1:1 random block allocation. The study was approved by the relevant Human Research Ethics Committee (ref: 15/101) and was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616001184460). The study protocol has been published elsewhere,[7] and an abbreviated description of the methods is presented below.

Participants. Eligible participants were 18 to 75 years of age, had grade 2 knee OA on radiograph according to the Kellgren-Lawrence scale,[8] and had moderate to severe unilateral knee pain that was resistant to at least six months of conservative treatment. Exclusion criteria included moderate to severe pain in other lower limb joints, prior ipsilateral knee surgery excluding arthroscopic surgery more than six months ago, and ipsilateral intra-articular injection in the last six months. A priori sample size calculations indicated that 29 participants were required per group to detect a 20% between-group difference for knee pain (power 80%, α 0.05). Recruitment occurred between July 2017 and November 2019.

Intervention. The intervention was conducted by one interventional radiologist (SL) who, at the outset of the trial, had four years of experience embolizing blood vessels for uncontrolled bleeding and had completed a TAE pilot study in ten people with knee pain and OA.[2]

Intervention group procedure. Participants in the intervention group received light sedation at the outset of the procedure followed by local anaesthetic injected into the groin immediately superficial to the femoral artery. A small incision was made at this site, a 3 F introducer sheath (Cook Medical, USA) inserted into the femoral artery and a 2.6 F microcatheter (Cook Medical) advanced to the origin of each genicular artery, and contrast medium was injected. Neovessels were embolized by injecting 0.5 g imipenem and cilastatin sodium (IPM-CS, Primaxin; Merck & Co, USA) that was suspended in 10 ml of iodinated contrast agent until blood flow stagnated on angiogram (Figure 1).

The intervention group procedure was adjusted early in the trial. Prior to commencing the study, and based on our pilot study,[2] it was planned that one major vessel, which was the primary contributor to neovascularization on angiogram, would be embolized. Consequently, the first four intervention group participants had one genicular artery embolized. While embolizing the fifth participant, the interventionalist (SL) discovered that additional neovessels from other previously 'normal' genicular arteries would spontaneously open on angiogram after embolization of the dominant geniculate. Hence, for the remaining intervention group participants (n = 25), all genicular arteries with collateral regional supply were sequentially assessed and embolized if neovessels were visible and accessible. In this group, eight participants' vascular anatomy prevented catheterization of one genicular artery, typically the superior medial genicular artery, due to the vessel's small diameter or acute direction change.

Control group procedure. Participants in the control group received the same light sedation as the intervention group at the outset of the procedure followed by local anaesthetic injected into the groin immediately superficial to the femoral artery. A small incision was made at this site. The interventionalist then pretended to complete the same procedure as received by the intervention group. Pre-recorded video images of an angiogram and embolization procedure were displayed on angiography monitors that the participant could see. The sham procedure lasted 30 to 60 minutes to match the duration of the real procedure.

All participants were monitored for four hours following the procedure and then discharged home. Adjunct treatments over the next 12 months, such as physiotherapy or pharmacotherapy, were recorded at each assessment, but not initiated or modified by the study investigators.

Outcomes. Outcomes were assessed pre-intervention and at one, six, and 12 months postintervention. A research assistant (RH), who was a physical therapist with more than 20 years' experience and trained by the study

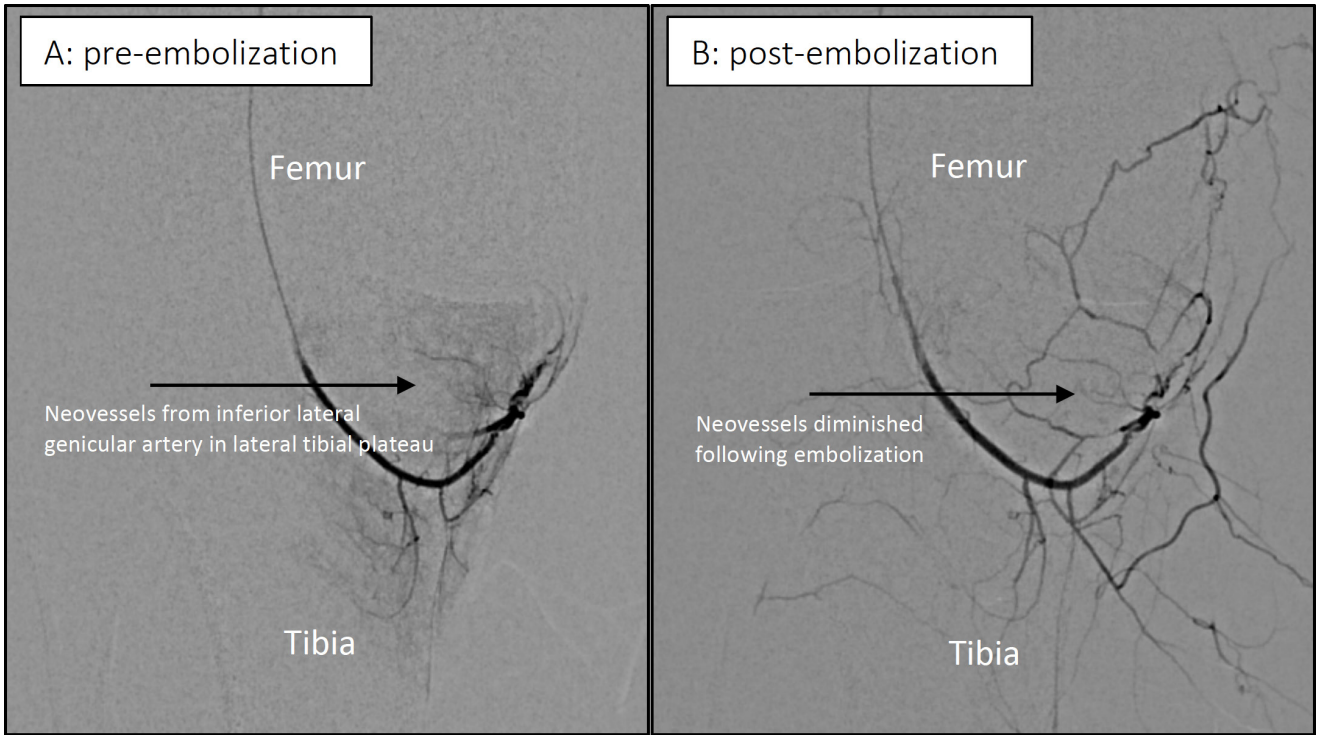


Fig. 1

Angiological findings a) before and b) after transcatheter arterial embolization. Pre-embolization findings demonstrate extensive neovasculature in the lateral tibial condyle that is absent postembolization.

investigators, collected study data according to the standardized protocol.

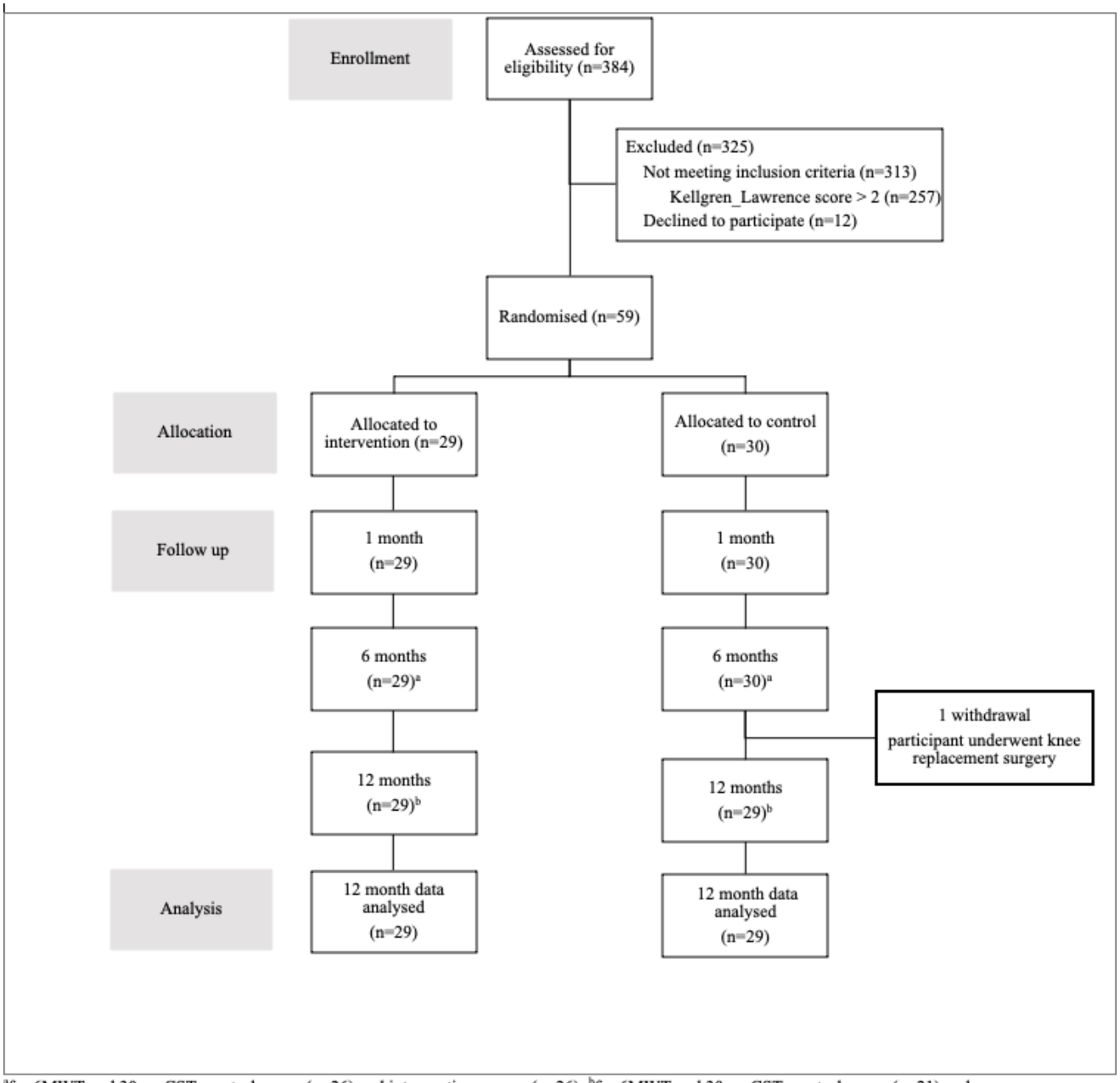
The primary outcome was knee pain at 12 months according to the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain scale.[9] Secondary outcomes were: 1) self-reported physical function (KOOS Function in Daily Living scale and KOOS Function in Sport and Recreation scale);[9] 2) self-reported quality of life (KOOS Quality of Life scale[9] and EuroQol five-dimension five-level questionnaire);[10] 3) self-reported knee joint stiffness (KOOS Symptoms scale);[9] 4) self-reported global change in knee pain (7-point Likert scale);[7] 5) six-minute walk test performance (6MWT);[11] 6) 30-second chair stand test performance (30CST);[12] 7) mental health (Hospital Anxiety Depression Scale (HADS));[13] 8) adverse events (Society of Interventional Radiology (SIR) Standards of Practice Committee adverse event classification);[14] and 9) change in pharmacotherapy to treat knee pain.

Knee MRI occurred at baseline and 12 months to assess for osteonecrosis. MRIs were reported by radiologists who were independent of the study. Most MRI's were reported by a musculoskeletal radiologist with at least 15 years' experience.

Data were entered by a research assistant (RH) into a secure, web-based data collection and management tool specifically designed for research.[15] Questionnaire data were double-entered by a second research assistant to identify and resolve any data entry errors.

Blinding. The participants, assessor (RH), and statistician (SMG) were blinded to group allocation. Due to the nature of the intervention, the interventionalist could not be blinded. Group allocation was concealed until immediately prior to the intervention. Each patient was informed of their group allocation by the interventionalist after the 12-month assessment. The statistician was unblinded after the primary and secondary data analyses but prior to subgroup analyses.

Statistical analysis. Intention-to-treat analyses were performed and included all participants as randomized and all available data. Descriptive data were summarized using frequencies (with percentages) for categorical data and means (with standard deviations (SDs)) for continuous/interval data or medians (with interquartile ranges (IQRs)) when data were skewed. Due to skewness, follow-up scores for continuous outcomes were compared between groups at each assessment (one, six, and 12 months) using quantile regression, adjusting for baseline scores. Global change was dichotomized into 'improved' (Likert score 'moderately better' or 'much better') or 'not improved' (Likert score 'slightly better' or below) and chi-squared tests were used to compare proportions between groups at each follow-up assessment. Similarly,



[a]for 6MWT and 30sec CST, control group (n=26) and intervention groups (n=26); [b]for 6MWT and 30sec CST, control group (n=21) and intervention group (n=26); reduced physical performance data due to COVID-19 social distancing restrictions preventing in-person assessment.

Fig. 2

Participant flow diagram. 6MWT, six-minute walking test; CST, chair stand test.

EQ-5D-5L scores were dichotomized into 'No/slight problem' and 'Moderate–Extreme problem', and proportions at each follow-up assessment were compared between groups using chi-squared tests. Subgroup analyses were performed to investigate if outcomes varied according to the extent of embolization performed. The intervention group was divided into three subgroups: complete embolization (n = 17), incomplete multi-vessel embolization (n = 8), and single-vessel embolization (n = 4). Scores at 12 months for the KOOS and Global Change were compared between the complete embolization group and control group as per our intention-to-treat analysis. All tests were two-sided and considered significant if the p-value was less than 0.05. Data were analyzed using Stata Statistical Package version 16 (StataCorp. 2019. Stata Statistical Software: Release 16, USA).

Table I. Participant characteristics.

Characteristic	Control (n = 30)	Intervention (n = 29)
Mean age, yrs (SD)	60.1 (7.7)	61.1 (8.0)
Female sex, n (%)	19 (63.3)	18 (62.1)
Median BMI, kg/m^2 (IQR)	33.6 (29.4 to 36.2)	30.2 (27.8 to 37.8)
Education (highest level completed), n (%)		
Primary school	19 (63.3)	19 (65.5)
Secondary school	5 (16.7)	4 (13.8)
University	6 (20.0)	6 (20.7)
Employment status, n (%)		
Working full-time	9 (30.0)	6 (20.7)
Working part-time	5 (16.7)	9 (31.0)
Looking for work	2 (6.7)	3 (10.3)
Retired	14 (46.7)	11 (37.9)
Comorbidities, n (%)		
Depression	8 (26.7)	9 (31.0)
Heart disease	7 (23.3)	5 (17.2)
Respiratory disease/smoker	4 (13.3)	4 (13.8)
Diabetes	2 (6.7)	6 (20.7)
Cancer	2 (6.7)	5 (17.2)
Osteoporosis/osteopenia	1 (3.3)	3 (10.3)
Neurological disorder	0	1 (3.5)
Median symptom duration, knee pain, yrs (IQR)	1.0 (1 to 3)	1.5 (1 to 5)
Mild pain in other parts of lower limbs* or lower back pain, n (%)	22 (73.3)	18 (62.1)

*Moderate to severe pain in other lower limb joints was an exclusion criteria.
IQR, interquartile range; SD, standard deviation.

Results

Participant flow and characteristics. A total of 59 participants were randomized and 58 provided questionnaire data at the 12-month assessment (Figure 2). No participant crossed over between groups during the 12-month follow-up period and no participant was unblinded. Due to COVID-19 restrictions affecting in-person contact during the data collection period, only 52 and 47 participants completed the physical performance measures at six and 12 months, respectively. Participant characteristics at the baseline assessment were similar between the groups and are presented in Table I. In summary, participants were typically older adults, almost two-thirds were female, and 92% were overweight or obese. Baseline median KOOS scores indicated moderate knee pain and moderate difficulty with daily activities. Baseline HADS scores suggested that 37% and 27% of participants would be diagnosed with anxiety and depression, respectively, based on a threshold score of ≥ 8.[13]

Intervention. All participants received the intervention or sham procedure as randomized. Neovessels were seen on angiogram in all intervention group participants (Figure 1).

Primary outcome. The primary outcome revealed no significant difference in KOOS pain scores at 12 months between the groups (Table II). Both groups' median KOOS pain scores improved over time; the control group improved by 29.4% and the intervention group by 41.3% at 12 months when compared to baseline scores.

Secondary outcomes. Secondary outcomes did not show significant differences between groups at one month, six months, and 12 months (Tables II and III, and Supplementary Material). Global change in knee pain at 12 months indicated that 17 participants (58.6%) in the intervention group reported being moderately or much better, compared to 11 participants (37.9%) in the control group, though this difference was not statistically significant (Table III).

Adverse events. No adverse events were reported at the time of the intervention. At the one-month assessment, five participants reported that bruising appeared at the groin near the incision site in the 24 hours following the procedure; four participants were in the intervention group and one in the control group. The bruising was considered a mild adverse event.[14] No osteonecrosis was evident on MRI at 12 months.

Subgroup analysis. For the intervention subgroups, outcomes improved progressively from single-vessel embolization (n = 4), to incomplete multivessel embolization (n = 8), and then complete embolization (n = 17) (Figure 3). This finding was consistent across all KOOS scales. Median KOOS scores at 12 months for the complete embolization group (n = 17) were significantly better than the control group (n = 29) for KOOS Sports and Recreation scale and KOOS Quality of Life scale (Table IV). For Global Change at 12 months, 76.5% of participants who received complete embolization were moderately

Table II. Between group comparisons of primary and secondary outcomes between the control (n = 30) and intervention (n = 29) groups.

	Baseline		1 mth			6 mths†			12 mths‡		
Outcome	**Control**	**Intervention**	**Control**	**Intervention**	**Difference (95% CI)***	**Control**	**Intervention**	**Difference (95% CI)***	**Control**	**Intervention**	**Difference (95% CI)***
Knee symptoms											
Median KOOS Pain (IQR)	47.2 (30.6 to 52.8)	47.2 (36.1 to 52.8)	63.9 (44.4 to 75.0)	63.9 (52.7 to 75.0)	0 (-13.4 to 13.4)	70.8 (50.0 to 91.7)	66.7 (44.4 to 77.8)	-2.6 (-21.8 to 16.7)	61.1 (47.2 to 88.9)	66.7 (52.8 to 88.9)	3.0 (-18.0 to 23.9)
Median KOOS Symptoms (IQR)	50.0 (35.7 to 57.1)	50.0 (39.3 to 60.7)	60.7 (50.0 to 75.0)	67.9 (57.1 to 75.0)	2.2 (-6.9 to 11.4)	64.3 (46.4 to 89.3)	60.7 (50.0 to 78.6)	-3.2 (-20.7 to 14.4)	57.1 (50.0 to 85.7)	75.0 (50.0 to 85.7)	9.3 (-7.2 to 25.8)
Physical function											
Median KOOS Sports/Rec (IQR)	27.5 (5.0 to 45.0)	20.0 (10.0 to 40.0)	42.5 (15.0 to 80.0)	45.0 (25.0 to 55.0)	0.4 (-23.2 to 23.9)	50.0 (15.0 to 75.0)	40.0 (25.0 to 65.0)	4.3 (-20.1 to 28.7)	35.0 (10.0 to 75.0)	45.0 (15.0 to 75.0)	12.5 (-15.8 to 40.8)
Median KOOS ADL (IQR)	53.7 (33.8 to 66.2)	50.0 (41.2 to 58.8)	69.9 (54.4 to 89.7)	72.1 (48.5 to 85.3)	-1.5 (-18.2 to 15.3)	78.7 (60.3 to 95.6)	72.1 (54.4 to 88.2)	-6.1 (-23.9 to 11.6)	70.6 (50.0 to 91.2)	72.1 (52.9 to 89.7)	7.4 (-9.2 to 23.9)
Median 6MWT (IQR)	378 (285 to 440)	386 (329 to 435)	416 (332 to 489)	420 (384 to 466)	13 (-34 to 59)	439 (302 to 494)	426 (335 to 480)	-18 (-62 to 25)	443 (360 to 480)	441 (361 to 486)	6 (-66 to 79)
Median 30-sec CST (IQR)	9 (7 to 12)	9 (8 to 11)	11 (8 to 14)	11 (9 to 13)	0.9 (-0.7 to 2.4)	11 (11 to 15)	112 (8 to 14)	-1.0 (-3.1 to 1.1)	12 (7 to 14)	12 (10 to 14)	0.8 (-2.2 to 3.7)
Quality of life											
Median KOOS QOL (IQR)	37.5 (6.3 to 43.8)	18.8 (12.5 to 31.3)	50.0 (25.0 to 62.5)	50.0 (25.0 to 62.5)	6.3 (-5.5 to 18.0)	53.1 (18.8 to 68.8)	37.5 (25.0 to 56.3)	6.3 (-11.2 to 23.7)	43.8 (25.0 to 62.5)	43.8 (25.0 to 68.8)	16.7 (-0.7 to 34.0)
Mental health											
Median HADS Anxiety (IQR)	6 (1 to 11)	6 (5 to 11)	5 (1 to 9)	4 (2 to 9)	-1.0 (-3.2 to 1.2)	4 (0 to 7)	7 (3 to 9)	1.0 (-1.1 to 3.1)	4 (1 to 7)	4 (2 to 9)	1.0 (-1.4 to 3.4)
Median HADS Depression (IQR)	4 (2 to 7)	5 (3 to 10)	3 (1 to 7)	4 (2 to 6)	0 (-1.9 to 1.9)	3 (1 to 6)	4 (2 to 6)	0 (1.7 to 1.7)	3 (1 to 6)	4 (1 to 6)	-1.0 (-3.2 to 1.2)

*Adjusted for baseline scores.
†For 6MWT and 30 sec CST, control group (n = 26) and intervention group (n = 26).
‡For 6MWT and 30 sec CST, control group (n = 21) and intervention group (n = 26).
ADL, activities of daily living; CI, confidence interval; CST, chair stand test; IQR, interquartile range; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; Rec, recreation.

Table III. Global change in knee pain between the control (n = 30) and intervention (n = 29) groups.

	1 mth			6 mths			12 mths		
Global change	**Control**	**Intervention**	**Difference***	**Control**	**Intervention**	**Difference***	**Control**	**Intervention**	**Difference***
Improved, n (%)	14 (46.7)	17 (58.6)	11.9%	12 (40.0)	15 (51.7)	11.7%	11 (37.9)	17 (58.6)	20.7%
Not improved, n (%)	16 (53.3)	12 (41.4)	-11.9%	18 (60.0)	14 (48.3)	-11.7%	18 (62.1)	12 (41.4)	-20.7%

*Intervention group minus control group, chi-squared tests p > 0.05 for between-group comparisons at 1 mth, 6 mths, and 12 mths.

or much better compared to 37.9% of participants in the control group (p = 0.012, chi-squared test).

Analgesia and concurrent treatments. At baseline, the proportion of participants taking any form of analgesia was similar between the groups (control 80%, intervention 72%; p = 0.494, chi-squared test). By the 12-month assessment, the proportion of participants taking analgesia was lower in the intervention group (control 48%, intervention 24%; p = 0.057, chi-squared test). Regarding concurrent treatments, six participants in the control group

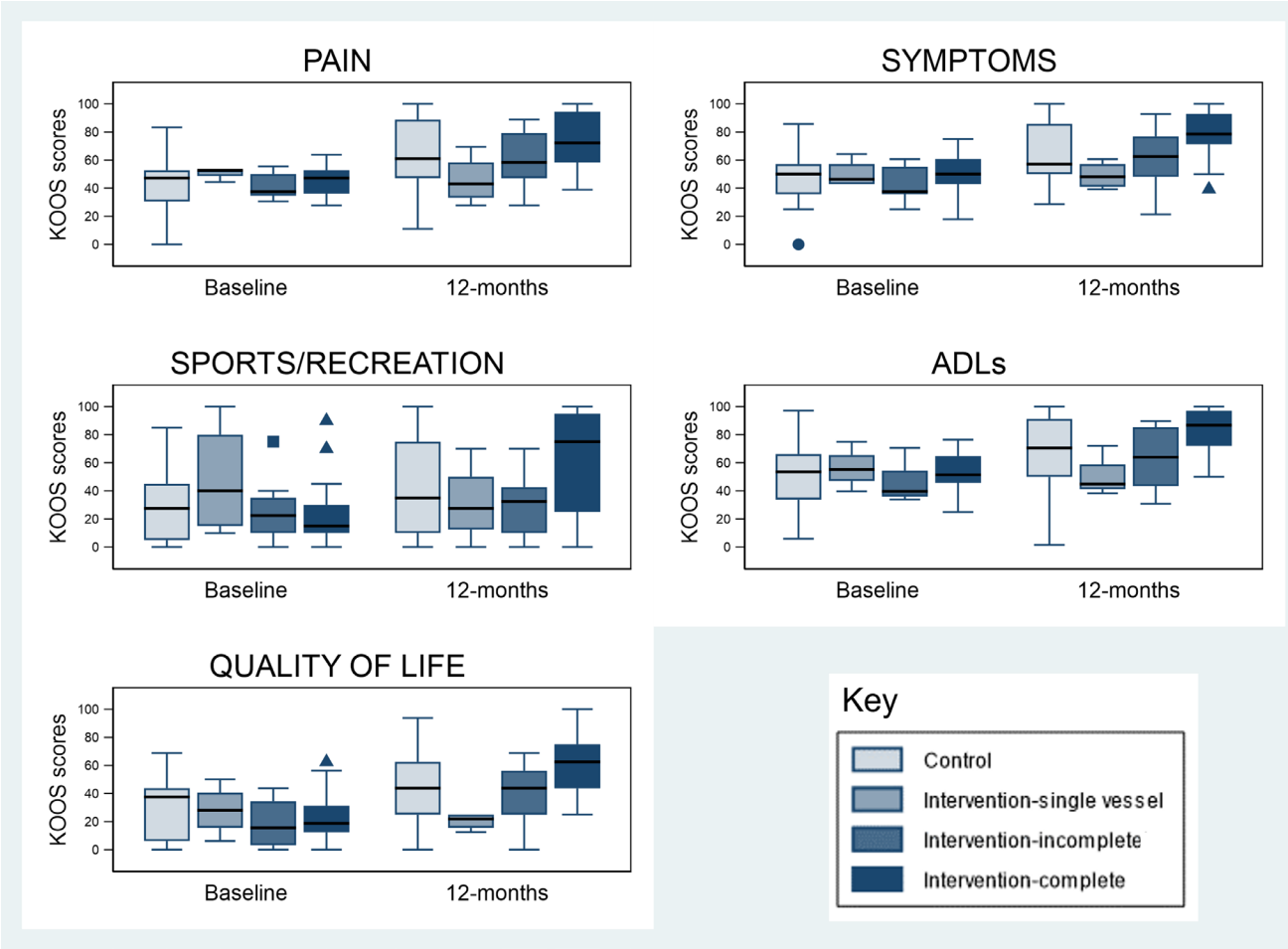


Fig. 3

Knee injury and Osteoarthritis Outcome Score (KOOS) outcomes by subgroup. ADLs, activities of daily living; intervention-single vessel = intervention group, one vessel embolized; intervention-incomplete = intervention group; incomplete multi-vessel embolization; intervention-complete = intervention group, all vessels embolized.

Table IV. Subgroup analysis: complete embolization (n = 17) compared to control group (n = 30) at 12 months.

Outcome	Baseline		12 mths		
	Control	Complete embolization	Control	Complete embolization	Difference (95% CI)*
Median KOOS Pain (IQR)	47.2 (30.6 to 52.8)	47.2 (36.1 to 52.8)	61.1 (47.2 to 88.9)	72.2 (58.3 to 94.4)	11.0 (-13.7 to 35.7)
Median KOOS Symptoms (IQR)	50.0 (35.7 to 57.1)	50.0 (42.9 to 60.7)	57.1 (50.0 to 85.7)	78.6 (71.4 to 92.9)	14.1 (-4.9 to 33.0)
KOOS Sports/Rec	27.5 (5.0 to 45.0)	15.0 (10.0 to 30.0)	35.0 (10.0 to 75.0)	75.0 (25.0 to 95.0)	48.5 (10.5 to 86.4)†
KOOS ADL	53.7 (33.8 to 66.2)	51.5 (45.5 to 64.7)	70.6 (50.0 to 91.2)	86.8 (72.1 to 97.1)	11.0 (-11.1 to 33.2)
KOOS QOL	37.5 (6.3 to 43.8)	18.8 (12.5 to 31.3)	43.8 (25.0 to 62.5)	62.5 (43.8 to 75.0)	25.0 (4.9 to 45.1)†

*Adjusted for baseline scores.
†$p < 0.05$.
ADL, activities of daily living; CI, confidence interval; IQR, interquartile range; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; Rec, recreation.

commenced a new treatment over the 12-month follow-up period (physiotherapy/exercise: n = 4, arthroscope: n = 1, knee brace: n = 1) and one additional participant had a total knee arthroplasty (TKA) after the six-month assessment and dropped out of the study. In the intervention group, 13 participants commenced a new treatment, none of which had surgery (physiotherapy/exercise: n = 12, corticosteroid injection: n = 1).

Discussion

To the best of our knowledge, this is the first randomized controlled study investigating one-year outcomes for TAE

versus a sham procedure in people with knee OA. No differences were found between groups for the primary and secondary outcomes. Subgroup analysis indicated that participants who received complete embolization, as distinct from partial embolization, had better global improvement, KOOS Sports and Recreation, and KOOS Quality of Life scores than the control group. No adverse events were recorded.

Participants in both the intervention and control group demonstrated substantial improvements in pain and function following the procedure. A recent systematic review of 11 studies of people undergoing TAE for OA-related knee pain determined that participants demonstrated a mean improvement at two years of 54% to 80% compared to baseline pain scores.[16] However, none of the studies except Bagla et al[17] included a comparison group, such that treatment-specific effects of TAE were unknown. Bagla et al[17] randomized 21 people to either TAE (n = 14) or a sham procedure (n = 7). The TAE group had significantly greater improvements in pain and function scores than the sham group at one month. However, the utility of the study is limited by 1) unknown medium- to long-term treatment-specific effects as participants were unblinded at one month when the sham group participants received TAE; 2) intention-to-treat analysis was not performed and participants who reported increased analgesia use (presumably due to increased pain) were removed from the analysis, which would have overestimated the beneficial effects of TAE; and 3) the small sample size creates uncertainty regarding the generalizability of the results to other participants and settings. Regardless, the one-month results presented by Bagla et al[17] contrast with our study; we found no difference between groups for our primary analysis. Participants in our control group demonstrated improvements in pain and function at one month, whereas Bagla et al's[17] control group remained largely unchanged. The 'placebo response' observed in our study, which is understood to be large and enduring in surgical and interventional trials, especially for subjective outcomes,[18] will have influenced our between-group comparisons. Previous studies indicated that this response might account for up to 78% of the effect of surgery or invasive procedures for painful conditions.[19] The implication for surgical or procedural trials including a sham group is that large treatment-specific effects or sample sizes are required to find differences between groups.

Subgroup analysis revealed superior outcomes for participants in the complete embolization group compared to the control group for three of the six outcomes analyzed, suggesting a possible dose-response effect. The KOOS Sports and Recreation and KOOS Quality of Life scales are the most sensitive KOOS scales for detecting effects at longer-term follow-up (i.e. ≥ one year) in people undergoing non-TKA surgery,[20] which could explain why these scales detected differences between the two groups despite the small sample size. The differences in KOOS scores between the groups were large and clinically meaningful. The patients' Global Change also indicated significant differences between groups, with twice as many intervention group participants reporting moderate to large improvements in knee pain compared to the control group, suggesting a clinically important difference. Dose-response relationships are known in arthritis pharmacology trials, and are an important criterion for establishing a cause-effect relationship.[21] However, subgroup analyzes increase the risk of Type I errors and spurious findings; hence, the results of our subgroup analysis should be viewed as exploratory and requiring confirmation in subsequent studies.

The potential mechanisms underlying a treatment-specific effect due to TAE are speculative. Neovascularization is common in painful musculoskeletal conditions. All participants in the current study had neovascularization on angiogram, which is consistent with most,[1,2,4,5] but not all,[3] TAE studies. Neovessels have been found throughout the OA joint including the synovium, meniscus, osteochondral junction, and articular cartilage.[22] Although angiogenesis is essential for growth, development, and tissue repair,[22] in chronic musculoskeletal pain neovessels are thought to be part of a pathological response that sustains inflammation and produces pain.[23] Sensory nerve growth accompanying neovessels might increase susceptibility to nociception, particularly in previously avascular and aneural structures such as articular cartilage and the inner regions of menisci.[22] TAE is suggested to disrupt the dysregulated inflammatory response by reducing the vascular transport of proinflammatory mediators and stimulation of sensory nerves.[24] Taguchi et al[25] induced adhesive capsulitis and neovascularization in rats. Following embolization, rats in the treatment group had fewer neovessels and mononuclear inflammatory cells, and greater running distance, than the sham group.

Adverse events following TAE for musculoskeletal conditions are infrequent and usually minor. Hinso et al[6] reviewed 19 studies and found transient skin discolouration and access site haematoma to be the most commonly reported adverse events in 9% and 6% of participants, respectively, which is consistent with our results. Tissue necrosis secondary to reduced vascularization is a potential serious adverse consequence of TAE. In our study and others, no evidence of osteonecrosis or ischaemic complications has been found on MRI up to two years following the procedure.[2-5]

This study is the largest RCT of TAE and the first with one-year follow-up. Risk of bias was reduced by: concealed allocation until immediately prior to the procedure; blinded patients, assessor, and statistician; almost complete follow-up for the primary outcome; and groups that were well matched at baseline for measured

characteristics. The OMERACT-OARSI core set of outcomes, including both self-report and performance-based measures were used.[26] Primary limitations include the relatively small sample size, which combined with substantial variance in outcomes within groups, reduced the statistical power of the study and increased the likelihood of Type 2 errors. Regardless, subgroup analysis found significant differences for two outcome measures, though at the risk of Type 1 errors. The intervention was modified in the study's early stages which reflected learning in the context of procedure's relatively recent application for treating musculoskeletal pain and limited published evidence to guide practice. Modifying the procedure allowed for subgroup analysis which indicated a possible dose-response effect. Following the procedure we monitored, but did not control, participants' use of medications or concurrent treatments which could have influenced outcomes. Similarly, prior to the intervention, participants were required to have completed at least six months of conservative treatment; however, we did not record how long prior to the intervention that these were completed, nor could we compare these treatments between the two groups. The study was single-site and employed a single interventionalist, which may affect the generalizability of these findings. Further research is required to evaluate the longer-term effects of TAE beyond 12 months.

In summary, TAE produced no significant benefit above placebo when the entire intervention group was compared to a sham procedure. Subgroup analysis suggested a dose-response relationship, providing conditional evidence of a treatment-specific effect when complete embolization was performed. Given the paucity of high-quality evidence around TAE, further comparative studies are required before definitive conclusions regarding the effectiveness of TAE can be made.

Take home message

- Transcatheter arterial embolization (TAE) produced no significant benefit above placebo when the entire intervention group was compared to a sham procedure.
- Subgroup analysis suggested a dose-response relationship. When complete embolization of all genicular arteries was performed, TAE produced benefits over placebo.
- Further comparative studies are required before definitive conclusions regarding the effectiveness of TAE can be made.

Supplementary material

EuroQol five-dimension five-level questionnaire scores, and Hospital Anxiety and Depression Scale scores.

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