CLINICAL SCIENCE

Exercise and education versus saline injections for knee osteoarthritis: a randomised controlled equivalence trial

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ABSTRACT

Objective To compare the efficacy of an exercise and education programme with open-label placebo given as intra-articular injections of inert saline on pain and function in individuals with knee osteoarthritis (OA).

Methods In this open-label, randomised controlled trial, we recruited adults aged ≥50 years with symptomatic and radiographically confirmed knee OA in Denmark. Participants were randomised 1:1 to undergo an 8-week exercise and education programme or four intra-articular saline injections over 8 weeks. Primary outcome was change from baseline to week 9 in the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire pain subscale (range 0 (worst)–100 (best)). Prespecified equivalence margins of ±8 KOOS pain points were chosen for the demonstration of comparable efficacy. Key secondary outcomes were the KOOS function and quality of life subscales, and patients' global assessment of disease impact.

Results 206 adults were randomly assigned: 102 to exercise and education and 104 to intra-articular saline injections. For the primary outcome, the least squares mean changes in KOOS pain were 10.0 for exercise and education and 7.3 for saline injections (difference 2.7 points, 95% CI −0.6 to 6.0; test for equivalence p=0.0008). All group differences in the key secondary outcomes respected the predefined equivalence margins. Adverse events and serious adverse events were similar in the two groups.

Conclusion In individuals with knee OA, an 8-week exercise and education programme provided efficacy for symptomatic and functional improvements equivalent to that of four open-label intra-articular saline injections over 8 weeks.

Trial registration number NCT03843931.

Key messages

What is already known about this subject?

- Exercise and education are recommended as the primary symptom management strategies for knee osteoarthritis (OA).
- No adequate placebo-controlled studies of exercise and education alone for knee OA exist.
- The isolated clinical effect of exercise and education has not been separated from that of a placebo intervention.

What does this study add?

- An exercise and education programme was equally effective as open-label application of inert intra-articular saline injections in providing symptomatic and functional improvements in individuals with knee OA.

How might this impact on clinical practice or future developments?

- These findings raise important questions about mechanisms of action as well as the continued widespread recommendation of exercise and education in the management of knee OA.

INTRODUCTION

Knee osteoarthritis (OA) is a highly and increasingly prevalent musculoskeletal condition causing pain, physical disability and reduced quality of life.[1] Exercise and education are recommended as the primary symptom management strategies based on numerous clinical trials.[2–4] In previous studies, multimodal physiotherapy (exercise, education, advice, gait aid, massage, taping and mobilisation) for knee and hip OA did not provide benefits over inert sham treatments.[5 6] However, no adequate placebo-controlled studies of exercise and education alone for knee OA exist probably due to unclear mechanisms of action, difficulties with blinding and the complexity of the intervention. Hence, the effect of exercise and education has not been separated from contextual factors, placebo and regression to the mean phenomena.

Recent advances in open-label placebo research have shown that considerable placebo responses can be elicited by inert substances if applied adequately.[7 8] Open-label placebo provides an opportunity to compare exercise and education with an inert comparator and thereby mitigate some of the inbuilt challenges with blinded comparator groups in clinical trials of exercise and education. Intra-articular saline injection is one such inert treatment and is commonly used as a comparator in clinical trials for knee OA. In indirect comparisons, the symptom response to saline injection was comparable to that of exercise in knee OA.[9–11]

In this trial, we took advantage of the potential of open-label application of inert treatments as comparator and conducted a randomised controlled trial where the aim was to assess if the efficacy of an exercise and education programme is equivalent to open-label placebo given as intra-articular injections of inert saline on pain and function in individuals with knee OA.

METHODS

Study design

We conducted an open-label, single centre randomised controlled trial with two parallel intervention groups. Evaluations and assessments took place in the OA outpatient's clinic at Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark, at baseline and at 9 and 12 weeks. Questionnaires were answered on a touch screen in the clinic. Links to online questionnaires were emailed weekly from baseline to week 8. The trial design and the trial protocol appears in online supplemental figure S1. The study was registered prospectively at www.ClinicalTrials.gov on 18 February 2019.

Participants

Between 30 July 2019 and 17 September 2020, participants were recruited from the OA outpatient's clinic at Bispebjerg-Frederiksberg Hospital. All participants provided written informed consent before participation.

Inclusion criteria were age ≥50 years, body mass index (BMI) of ≤35 kg/m^2, meeting the American College of Rheumatology clinical classification of knee OA,[12] average knee pain during weight-bearing activities in the last week of ≥4/10, radiographically verified tibiofemoral OA (Kellgren-Lawrence grade ≥2).[13] Major exclusion criteria were intra-articular treatments of any kind in either knee and participation in exercise therapy within 3 months of the baseline visit (for details, see online supplemental file).

Potential participants were informed about the trial by an investigator who obtained written informed consent and coordinated trial inclusion. Information was delivered neutrally, ensuring that descriptions of both interventions were promoted equally including that the investigators had no treatment preference (clinical equipoise).[11] Saline injections were described as inert, yet with potential beneficial effects that may compare to those of exercise and education. The participants were informed that 'active ingredients' in both interventions are unverified and involves the sum and interaction of many factors.[11] The most symptomatic knee at baseline was chosen as the study knee.

Interventions

Full details of the interventions are in the published protocol[11] and the online supplemental file.

The *exercise and education programme* consisted of the Good Life with osteoArthritis in Denmark (GLAD) programme.[14] GLAD is an 8-week structured treatment programme consisting of patient education and supervised neuromuscular exercise for people with symptomatic knee or hip OA.[14] In this trial, GLAD was delivered by GLAD-certified physiotherapists at the department of physiotherapy at Bispebjerg-Frederiksberg Hospital.

Two group-based educational sessions lasting about 1.5 hours were provided, addressing knowledge on knee OA, treatment options with a focus on exercise and its benefits, and advice about self-management.[14] The exercise part of GLAD was delivered as 12 1-hour, group-based, individually supervised sessions, two times per week for 6 weeks. Satisfactory treatment adherence was defined as attendance to at least one educational (50%) and eight exercise sessions (75%).

Intra-articular saline injections of 5 mL isotonic solution of sodium chloride in sterile water (0.9%=9 mg/mL) were given into the study knee at weeks 1, 3, 5 and 7 after baseline. Injections were performed using ultrasound imaging guidance[15] (Logic E9; General Electrics Medical System, Milwaukee, Wisconsin, USA) by two physiotherapists with 7 and 15 years of experience in ultrasound-guided intra-articular injections, under supervision and regulation by a senior rheumatologist (HB). The procedure was documented in real time, ensuring correct deposition of the bolus in the joint cavity. No local analgesics were used during the procedure. If excessive joint fluid was detected, it was aspirated if possible and deemed clinically relevant, prior to injection of the saline. Satisfactory treatment adherence was defined as reception of at least three injections (75%).

For all participants, mild analgesics (paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid) were allowed, while initiation of opioids, glucocorticoids and off-protocol intra-articular injections were not allowed.

Primary outcome

The primary outcome was the change from baseline in the pain subscale of the Knee injury and Osteoarthritis Outcome Score questionnaire (KOOS)[16] at week 9. KOOS consists of five subscales: pain, physical function, knee-related quality of life, sports and recreation, and symptoms. Each subscale consists of multiple items with scores ranging from 0 to 100 (worst to best).

Key secondary and secondary outcomes

Key secondary outcomes were changes from baseline in the KOOS physical function and knee-related quality of life subscales, and the participant's global assessment of the impact of OA on overall life assessed using a 100 mm Visual Analogue Scale (VAS) (higher is worse). Other secondary outcomes included changes from baseline in the KOOS sports and recreation and symptoms subscales, and physical performance by the 4×10 m fast walk test (seconds),[17] stair ascend and descend test (seconds),[17] and the number of chair stands in 30 s,[17] as well as treatment response according to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International(OMERACT-OARSI) criteria.[18]

Safety and exploratory outcomes

Safety outcomes included swollen study knee (present/absent) by examination of palpable knee effusion judged by a rheumatologist.[19] Also, study knee effusion was visualised (present/absent) by ultrasound and aspirated joint fluid was recorded (millilitre). The exploratory outcomes included use of acetaminophen and NSAIDs recorded at baseline and week 9, and the Intermittent and Constant Osteoarthritis Pain questionnaire[20] with two subscores, constant pain and intermittent pain on 0–100 scales (best to worst). Further, average morning pain during the past week was assessed using a 100 mm VAS (higher is worse). Adverse and serious adverse events were registered at clinical visits and by spontaneous reports from the participants (see protocol).

Randomisation and blinding

Before randomisation, demographic information and all baseline measures were obtained.

Participants were assigned 1:1 to either exercise and education or saline injections according to a computerised randomisation

list based on permuted random blocks of variable size (2–6) generated before enrolment. Allocation sequence was developed by the trial biostatistician not actively involved in the conduct of the trial. Allocation was stratified by BMI of ≥30 kg/m^2, swollen study knee on palpation,[19] evidence of bilateral tibiofemoral OA (Kellgren-Lawrence grade ≥2) and participation in sports activities as a young adult (20s). Allocation was concealed until an investigator pressed 'randomise' in the electronic trial management system.

As this was an open-label trial neither health professionals delivering the interventions, nor participants were blinded to treatment allocation. Outcome assessors were blinded to allocation where possible, and participants were requested not to disclose allocation during assessments.

Sample size

The sample size was calculated for test of equivalence of the groups at 90% power and an alpha level of 0.05 using two one-sided tests (one-sided alpha of 0.025) with equivalence margins of ±8 KOOS pain points, assuming a mean difference of 0 and a common SD of 15 points. From this, a total sample size of 154 participants was required. To account for dropout, the sample size was a priori increased to 200 participants.

Statistical analysis

The analysis was performed according to the a priori statistical analysis plan that was publicly available online (www.clinicaltrials.gov) before the last participant's last visit (see online supplemental file).

The primary analysis was performed using the intention-to-treat (ITT) population; patients were assessed and analysed as members of their randomised groups, irrespective of adherence to the treatments. Continuous outcomes were analysed as change from baseline using repeated measures mixed linear models, including participants as random effects, with fixed effect factors for group and week (including all timepoints to respect the ITT principle) and the corresponding interaction, while adjusting for baseline values (to increase precision) and the stratification factors (as part of the design). Results are reported as least squares means and SEs, and differences between least squares means are reported with two-sided 95% CIs. The group difference in the primary outcome was assessed for equivalence by a two one-sided test of equivalence with alpha 0.025 assessing if the 95% CI respects the predefined equivalence margin of ±8 KOOS pain points. No explicit adjustments for multiplicity were applied; rather the key secondary outcome measures were analysed in a prioritised order. Missing data were handled implicitly in the ITT analysis by the mixed linear models.[21] Sensitivity analyses[22] were performed for the primary and key secondary outcomes at week 9 by repeating the primary analyses on the per-protocol population predefined as participants with satisfactory adherence and without major protocol deviations. Further, analysis of covariance with multiple imputation of missing data adjusted for stratification factors and baseline values was performed followed by analysis of covariance with a baseline observation carried forward imputation of missing data. If the primary analysis and the sensitivity analyses confirm each other, confidence in the results is increased both regarding equivalence and superiority claims. All analyses were performed in SAS V.9.4.

Patient and public involvement

Two patient research partners (one female and one male) were involved in designing and preparing the study, including review and revision of the protocol and patient information. They acknowledged the idea and purpose of the study and participated in discussions of ethics, design, choice of outcomes, relevance and feasibility of the trial. They worked voluntarily and have been offered coauthorship of trial-related publications. Both declined coauthorship of the present publication. Hence, they did not review this manuscript.

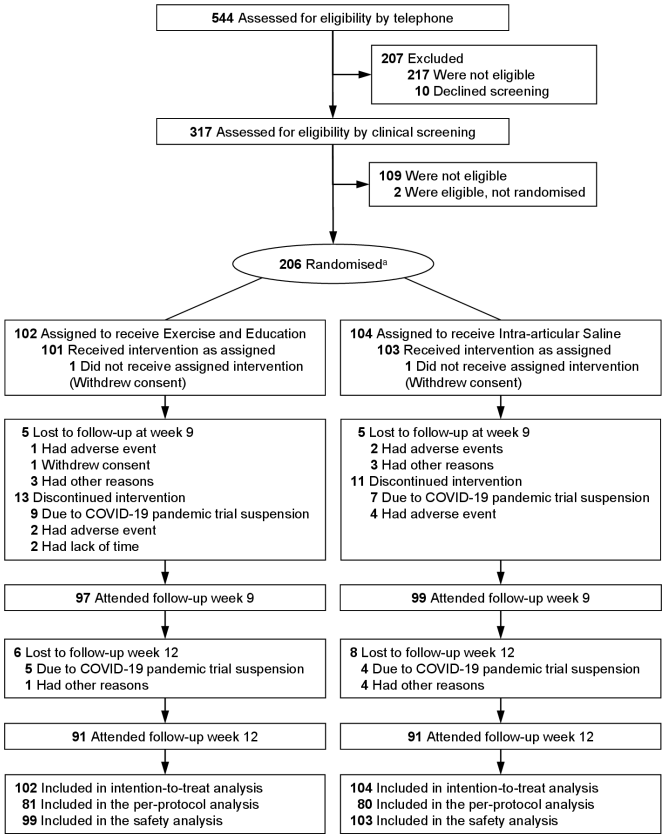

Figure 1 Flowchart of participants throughout the study. A stratified block randmisation method, stratified by BMI ≥30 kg/m2 (yes/no), swollen study knee upon palpation, evidence of bilateral tibiofemoral osteoarthritis assessed as Kellgren-Lawrence grade ≥2, and participation in sports activities as a young adult (20s).

RESULTS

Participants

From 30 July 2019 through 17 September 2020, 317 individuals were screened for eligibility (figure 1); 109 were ineligible for inclusion; and 2 eligible individuals chose not to be randomised. Thus, 206 subjects underwent randomisation; 102 (49.5%) were assigned to exercise and education and 104 (50.5%) to intra-articular saline. The mean age was 68.4 years; 54% were men; and the mean BMI was 27.3. Baseline characteristics were similar in the two groups (table 1). Participants in the exercise and education group attended on average 11.1 (79.3%) sessions out of possible 14 (range 0–14) sessions. Participants in the saline group received on average 3.4 (84.9%) injections out of possible 4 (range 0–4).

Primary outcome

The mean changes (±SE) in KOOS pain score from baseline to week 9 were 10.0±1.5 in the exercise and education group and 7.3±1.5 in the intra-articular saline group (group difference: 2.7 points, 95% CI −0.6 to 6.0; p=0.1122 for test of

Table 1 Baseline characteristics of the participants

	Exercise and education	Intra-articular saline
	n=102	n=104
Characteristics		
Age (years)	70.1±8.3	66.7±8.2
Male sex, n (%)	57 (55.9)	55 (52.8)
Body mass (kg)	80.7±14.2	81.5±13.9
Height (cm)	172.0±9.5	172.1±9.5
BMI*	27.2±3.7	27.4±3.6
Kellgren-Lawrence score, n (%)†		
2	25 (24.5)	31 (29.8)
3	36 (35.3)	30 (28.9)
4	41 (40.2)	43 (41.3)
Stratification factors, n (%)		
BMI ≥30	25 (24.5)	25 (24.0)
Swollen study knee	35 (34.3)	37 (35.6)
Bilateral tibiofemoral OA (K/L ≥2)	92 (90.2)	93 (89.4)
Active as a young adult	66 (64.7)	68 (65.4)
KOOS‡		
Pain††	56.3±14.9	57.6±13.1
Physical function in activities of daily living‡‡	65.7±15.0	67.8±14.7
Quality of life‡‡	39.7±15.5	40.8±14.6
Symptoms	64.0±17.1	62.8±16.3
Physical function in sports and recreation	35.2±21.3	31.8±19.6
Patient Global Assessment (mm)§‡‡	61.4±20.9	59.2±20.5
Morning pain (mm)¶	44.7±25.4	44.5±23.4
ICOAP scores**		
Constant pain subscore	23.6±28.4	15.4±23.8
Intermittent pain subscore	40.8±22.3	42.9±18.1
Total score	33.0±19.2	30.4±15.0
Performance tests		
4×10 m fast walk test (s)	26.6±5.3	25.5±6.5
30 s chair stand test (repetitions)	12.3±3.6	12.4±3.6
Stair climbing test (s)	15.2±5.9	13.9±8.0
Clinical assessment		
Swollen study knee, clinical, n (%)‡‡	35 (34.3)	37 (35.6)
Analgesics use		
Paracetamol or NSAID user, n (%)	34 (33.3)	43 (41.4)

Plus–minus values are means±SD unless otherwise stated.
*The BMI is the weight in kilogram divided by the square of the height in metre.
†Scores on the Kellgren-Lawrence scale range from 0 to 4, with a score of 2, 3 or 4 indicating definite OA and higher scores indicating more severe disease.
‡Scores on KOOS subscales range from 0 (worst) to 100 (best).
§Patient Global Assessment is a VAS relating to the degree of the patient's perceived impact of knee OA on overall life (with scores ranging from 0 to 100); higher scores indicate higher disease impact.
¶Morning pain is a VAS relating to the degree of the patient's perceived averaged morning knee pain during the last week (with scores ranging from 0 to 100); higher scores indicate more pain.
**Scores on ICOAP ranges from 0 (no pain) to 100 (extreme pain).
††Primary outcome measure.
‡‡Key secondary outcome measure.
BMI, body mass index; ICOAP, Intermittent and Constant Osteoarthritis Pain; K/L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; VAS, Visual Analogue Scale.

superiority). The 95% CI of the group difference in change in KOOS pain from baseline to week 9 respected the predefined equivalence margin of ±8 points (p=0.0008 for equivalence, table 2). The trajectories of the KOOS pain subscale are illustrated in figure 2.

Secondary and other outcomes

In the key secondary outcomes, the estimated treatment differences between groups at week 9 were 0.8 points (95% CI −2.3 to 4.0) for KOOS function score; 1.8 points (95% CI −1.5 to 5.2) for KOOS quality of life score; and 5.7 mm (95% CI −11.3 to −0.1) for Participant Global Assessment (table 2). The key secondary outcomes all respected the predefined criteria for equivalence (see statistical analysis plan), although the group difference in the Participant Global Assessment was statistically in favour of the exercise and education group.

Numbers, rates and severity of adverse events and their relationship to trial treatment were similar across groups (table 3). Serious adverse events rate was similar, and none were related to the treatments.

Finally, the results in the primary and key secondary outcomes appeared stable (unchanged) at week 12 (online supplemental table S1). There were no differences between groups in the other secondary, safety and exploratory outcomes at week 9 (table 2) and week 12 (online supplemental table S1). The overall pattern of results for all outcomes was not changed in the sensitivity analyses (online supplemental tables S2-S4).

DISCUSSION

This study found that an exercise and education programme provided improvements in knee pain equivalent to that of inert intra-articular saline in the short term (9–12 weeks) in individuals with knee OA. The 95% CI of the group difference in KOOS pain change from baseline to week 9 was within our predefined equivalence margin of ±8 points. The key secondary and other secondary outcomes that evaluated patient-reported outcomes and physical performance corroborate the results of the primary outcome and met the predefined criteria for equivalence based on minimal clinically important differences. Treatment adherence was similar in the two groups, as were adverse and serious adverse events. None of the serious adverse events appeared related to the study treatment.

Over the past decades, more than 100 clinical studies on exercise for knee OA have shown beneficial effects as compared with no-treatment control groups,[23] which has resulted in strong recommendations of exercise as primary management strategy of knee OA.[2–4] However, comparison to no-treatment control groups induces a significant risk of bias and precludes assessment of the contribution of contextual factors, placebo and regression to the mean phenomena. This study is the first to compare a widely implemented exercise and education programme with an open-label placebo, and the results show that the exercise and education programme provides equal effects as an open-label application of intra-articular saline known to be associated with contextual factors and placebo responses.[9 10] Few studies have applied inert or sham comparators and those that do suggest that multimodal physical therapy (mixing exercise and other physiotherapeutic techniques) does not confer additional benefits in hip and knee OA.[5 6] Recently, the Strength Training for Arthritis Trial (START) study[24] showed that 18 months of muscle strengthening exercise for patients with knee OA were not more effective than an attention control group, suggesting that improvements in OA pain secondary to exercise are mainly driven by placebo response phenomena, contextual factors, natural course of the disease and regression to the mean, also suggested by others.[25] Our study corroborates this as the neuromuscular exercise and education intervention we delivered did not provide benefits that exceed those of inert saline injections.

In line with this, a possible explanation for the beneficial effects of exercise and education relates to the considerable contact time with clinicians (up to 15 hours with a physical therapist over 8 weeks), which is known to augment improvement in outcomes.[26–28] Likewise, the invasiveness of the procedures associated with intra-articular injections is known to provide strong placebo responses,[28–30] and it is possible that the placebo response to intra-articular saline is higher than

Table 2 Primary, secondary, safety and exploratory outcomes at primary endpoint, week 9 in the intention-to-treat population

	Exercise and education (n=102)	Intra-articular saline (n=104)	Estimated treatment difference	
	LSMean (SE)	LSMean (SE)	ΔLSMean (95% CI)	P value
Primary outcome				
Change in KOOS pain score, equivalence test†	10.0±1.5	7.3±1.5	2.7 (–0.6 to 6.0)	0.0008
Change in KOOS pain score, superiority test†				0.1122
Key secondary outcomes				
Change in KOOS function score	6.9±1.4	6.0±1.4	0.8 (–2.3 to 4.0)	
Change in KOOS quality of life score	8.0±1.5	6.2±1.5	1.8 (–1.5 to 5.2)	
Change in PGA–VAS (mm)	–19.8±2.6	–14.1±2.5	–5.7 (–11.3 to –0.1)	
Other secondary outcomes				
Change in KOOS sports and recreation score	8.0±2.1	9.0±2.1	–1.0 (–5.5 to 3.5)	
Change in KOOS symptoms score	6.2±1.6	8.0±1.5	–1.8 (–5.2 to 1.6)	
OMERACT-OARSI responders, n (%)*‡	44 (42.9)	32 (31.0)	9.6 (–6.6 to 24.1)¶	
Change in 4×10 m fast walk test (s)	–0.5±0.3	–0.5±0.3	0.1 (–0.5 to 0.7)	
Change in 30 s chair stand test (repetitions)	0.4±0.2	–0.1±0.2	0.5 (–0.1 to 1.0)	
Change in stair climbing test (s)	–1.2±0.3	–0.6±0.3	–0.5 (–1.2 to 0.1)	
Safety outcomes				
Swollen study knee, clinical, n (%)‡	40 (38.9)	32 (30.7)	8.2 (–11.2 to 27.8)¶	
Study knee effusion, ultrasound, n (%)‡	35 (34.4)	24 (23.2)	9.4 (–8.6 to 28.2)¶	
Study knee aspiration volume (mL)§	18.5±6.0	25.6±9.3	–7.1 (–24.3 to 10.1)	
Exploratory outcomes				
Change in average morning pain–VAS score (mm)	–14.9±2.5	–18.7±2.4	3.8 (–1.8 to 9.4)	
Change in ICOAP total score	–8.3±1.7	–8.3±1.6	0.0 (–3.7 to 3.7)	
Change in ICOAP constant pain subscore	–9.8±2.4	–6.7±2.3	–3.1 (–8.5 to 2.3)	
Change in ICOAP intermittent pain subscore	–8.1±2.2	–9.6±2.1	1.5 (–3.4 to 6.3)	
Paracetamol and NSAID discontinued, n (%)‡	11 (10.3)	10 (10.1)	–0.6 (–8.3 to 27.3)¶	
Treatment adherence				
Treatment adherence (%), mean (SD)	79.3 (29.0)	84.9 (24.7)	5.5 (–12.9 to 1.9)**	
Treatment adherers, n (%)	85 (83.3)	87 (83.7)	–0.3 (–13.3 to 7.8)¶	

Values are LSMean±SE unless otherwise stated.
*OMERACT-OARSI responder score is a single dichotomous variable based on changes after treatment in three symptomatic domains (pain, function and patient's global assessment).
†Primary outcome was analysed using both a test for equivalence and a test for superiority.
‡Missing data in binary outcomes were handled using an extreme-set multiple imputation technique followed by applying Rubin's rule to both the observed and four extreme case scenarios: (1) data as observed, (2) worst–worst case, (3) worst–best case, (4) best–worst case and (5) best–best case scenario.
§Aspiration only performed in case of effusion detected on ultrasound.
¶Adjusted risk difference with 95% CI (%).
**Mean difference (95% CI).
ICOAP, Intermittent and Constant Osteoarthritis Pain; KOOS, Knee Injury and Osteoarthritis Outcome Score; LSMean, least squares mean; NSAID, non-steroidal anti-inflammatory drug; PGA, Patient Global Assessment; VAS, 100 mm Visual Analogue Scale.

that of exercise and education. On the other hand, the within-group effect size for saline injections in this trial was slightly smaller than those reported in clinical trials where saline was used as a placebo comparator,[9 10] likely due to the open-label design of this trial compared with the double-blinded methodology in the other trials. In contrast, the within-group effect size for exercise and education is similar to those reported in previous clinical trials.[31]

Limitations and strengths of this study

There are limitations to this study. First, the dissimilarities of the two interventions can be argued to limit their comparability. However, due to the inherent unblindable nature and unknown 'active components' of exercise and education, it is not possible to deliver a completely inactive version. We sought to bypass this by applying an open-label study design and comparing exercise and education to intra-articular saline that is commonly used as placebo comparator and easier to monitor than oral or topical placebos. Despite this, the separation of specific and contextual effects of both treatments remains unclear. Second, we only assessed short-term efficacy. However, a similar exercise intervention with longer duration (12 weeks)[32] provided a similar response as the present, and the 18 months of efficacy of exercise were not superior to attention control in the recent START study.[24] The GLAD programme includes an encouragement of the patients to continue exercise on their own, and it is suggested that the effects are sustained for up to 1 year.[33] On the other hand, the effects of intra-articular saline have also been suggested to be sustainable in the long term (6–12 months),[9] and our results add to the discussion of the inertness of saline injections, as potential physiological effects have been suggested.[9 10]

The strengths of this trial include the relatively large sample size and the equivalence design, which increase the precision of the estimated group differences. A rather conservative equivalence margin of ±8 points for the KOOS pain subscale was chosen as this is the suggested threshold for minimal clinically important difference.[34] A less conservative ±10-points

Table 3 Adverse events in the safety population defined as participants in the intention-to-treat population who have received at least one intra-articular injection (intra-articular saline group) or attended at least one exercise session (exercise and education group)

	Exercise and education (n=99)	Intra-articular saline (n=103)
Exposure time (patient weeks)	1131	1175
AE, n patients (%)	34 (34%)	40 (39%)
AE, n events (rate–events per patient week)	49 (0.04)	48 (0.04)
AEs leading to discontinuation, n patients (%)	2 (2%)	4 (4%)
Maximum reported severity of AEs, n (%)		
Mild, n patients	16 (16%)	22 (21%)
Moderate, n patients	12 (12%)	14 (14%)
Severe, n patients	6 (6%)	4 (4%)
AEs, relationship to trial treatment, n events (rate–events per patient week)		
Not related	12 (0.01)	3 (0.003)
Probably not related	9 (0.01)	18 (0.015)
Probably related	28 (0.02)	27 (0.02)
AEs, classification, n events (rate–events per patient week)		
Infections and infestations	3 (0.003)	0 (0)
General disorders and administrative site conditions	5 (0.004)	6 (0.005)
Musculoskeletal and connective tissue disorders	34 (0.03)	38 (0.03)
Skin and subcutaneous tissue disorders	0 (0)	3 (0.003)
Injury, poisoning and procedural complications	7 (0.006)	1 (0.001)
SAE, n patients (%)	5 (5%)	5 (5%)
SAE, n events (rate–events per patient week)	9 (0.008)	5 (0.004)
SAEs leading to discontinuation, n patients (%)	0 (0%)	0 (0%)
SAEs, relationship to trial treatment, n events (rate–events per patient week)		
Not related	1 (0.001)	3 (0.003)
Probably not related	8 (0.007)	2 (0.002)
Probably related	0 (0)	0 (0)
Deaths, n events (rate–events per patient week)	0 (0)	0 (0)

The severity of an AE refers to the maximum intensity of the event. An event was considered severe (compared with mild or moderate) if it interfered substantially with the patients' usual activities. An AE was classified as serious if it was fatal or life-threatening, required inpatient hospitalisation, caused significant disabling, or required medical intervention to prevent permanent impairment or damage.
AE, adverse event; SAE, serious adverse event.

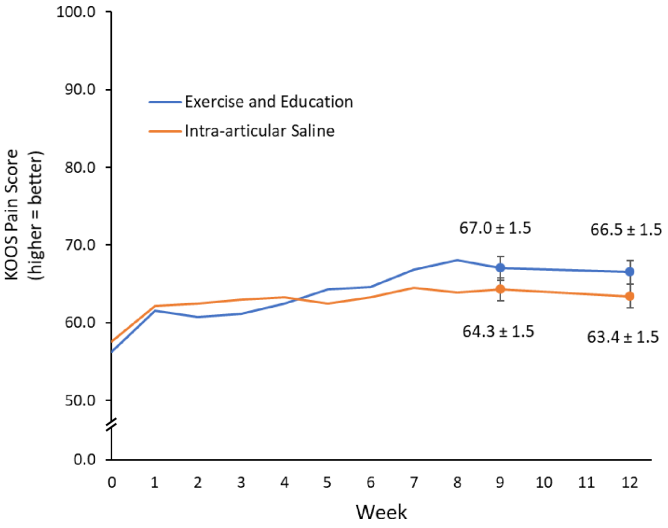

Figure 2 Trajectories of the KOOS pain subscale in the intention-to-treat population. High values represent less pain; low values represent more pain. Data points represent least squares means; error bars, SE. KOOS, Knee Injury and Osteoarthritis Outcome Score.

margin has been used previously to indicate absence of a clinically meaningful difference between anterior cruciate ligament reconstruction and structured rehabilitation.[35] Further, baseline characteristics of our participants and changes in the exercise and education group are on par with those reported from 28 370 patients following implementation of GLAD in real-world clinical practice on three different continents.[36] Also, we delivered the exercise and education intervention according to the GLAD standards. This altogether documents the fidelity of our trial intervention and worldwide generalisability of the results.

CONCLUSION

Among individuals with knee OA, an 8-week exercise and education programme provided efficacy for symptomatic and functional improvements equivalent to that of open-label application of intra-articular inert saline injections. These findings raise important questions about mechanisms of action as well as the continued widespread recommendation of exercise and education in the management of knee OA.

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REFERENCES

1 Sharma L. Osteoarthritis of the knee. *N Engl J Med* 2021;384:51–9.
2 Bannuru RR, Osani MC, Vaysbrot EE, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
3 Kolasinski SL, Neogi T, Hochberg MC, *et al*. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2020;72:149–62.
4 Fernandes L, Hagen KB, Bijlsma JWJ, *et al*. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–35.
5 Bennell KL, Egerton T, Martin J, *et al*. Effect of physical therapy on pain and function in patients with hip osteoarthritis: a randomized clinical trial. *JAMA* 2014;311:1987–97.
6 Bennell KL, Hinman RS, Metcalf BR, *et al*. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. *Ann Rheum Dis* 2005;64:906–12.
7 Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ* 2018;363:k3889.
8 Blease CR, Bernstein MH, Locher C. Open-label placebo clinical trials: is it the rationale, the interaction or the pill? *BMJ Evid Based Med* 2020;25:159–65.
9 Altman RD, Devji T, Bhandari M, *et al*. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: a systematic review and meta-analysis of randomized trials. *Semin Arthritis Rheum* 2016;46:151–9.
10 Saltzman BM, Leroux T, Meyer MA, *et al*. The therapeutic effect of intra-articular normal saline injections for knee osteoarthritis: a meta-analysis of evidence level 1 studies. *Am J Sports Med* 2017;45:2647–53.
11 Bandak E, Overgaard AF, Kristensen LE, *et al*. Exercise therapy and patient education versus intra-articular saline injections in the treatment of knee osteoarthritis: an evidence-based protocol for an open-label randomised controlled trial (the Disco trial). *Trials* 2021;22:18.
12 Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis & Rheumatism* 1986;29:1039–49.
13 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494–502.
14 Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D™): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord* 2017;18:72.
15 Qvistgaard E, Kristoffersen H, Terslev L, *et al*. Guidance by ultrasound of intra-articular injections in the knee and hip joints. *Osteoarthritis Cartilage* 2001;9:512–7.
16 Roos EM, Roos HP, Lohmander LS, *et al*. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.
17 Dobson F, Hinman RS, Roos EM, *et al*. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1042–52.
18 Pham T, Van Der Heijde D, Lassere M, *et al*. Outcome variables for osteoarthritis clinical trials: the OMERACT-OARSI set of Responder criteria. *J Rheumatol* 2003;30:1648–54.
19 Maricar N, Callaghan MJ, Parkes MJ, *et al*. Interobserver and intraobserver reliability of clinical assessments in knee osteoarthritis. *J Rheumatol* 2016;43:2171–8.
20 Hawker GA, Davis AM, French MR, *et al*. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409–14.
21 Detry MA, Ma Y. Analyzing repeated measurements using mixed models. *JAMA* 2016;315:407–8.
22 Little RJ, D'Agostino R, Cohen ML, *et al*. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012;367:1355–60.
23 Bartholdy C, Nielsen SM, Warming S, *et al*. Poor replicability of recommended exercise interventions for knee osteoarthritis: a descriptive analysis of evidence informing current guidelines and recommendations. *Osteoarthritis Cartilage* 2019;27:3–22.
24 Messier SP, Mihalko SL, Beavers DP, *et al*. Effect of high-intensity strength training on knee pain and knee joint compressive forces among adults with knee osteoarthritis: the start randomized clinical trial. *JAMA* 2021;325:646–57.
25 Englund M. Bout of the corner men and not the boxers? contextual effects flex their muscles. *Ann Rheum Dis* 2018;77:159–61.
26 Bennell KL, Hunter DJ. Physical therapy before the needle for osteoarthritis of the knee. *N Engl J Med* 2020;382:1470–1.
27 Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord* 2018;19:27.
28 Zhang W, Robertson J, Jones AC, *et al*. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008;67:1716–23.
29 Bannuru RR, Schmid CH, Kent DM, *et al*. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162:46–54.
30 Bannuru RR, McAlindon TE, Sullivan MC, *et al*. Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials. *Ann Intern Med* 2015;163:365–72.
31 Fransen M, McConnell S, Harmer AR, *et al*. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015;1:CD004376.
32 Henriksen M, Christensen R, Klokker L, *et al*. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial. *JAMA Intern Med* 2015;175:923–30.
33 Skou ST, Bricca A, Roos EM. The impact of physical activity level on the short- and long-term pain relief from supervised exercise therapy and education: a study of 12,796 Danish patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2018;26:1474–8.
34 Roos EM, Lohmander LS. The knee injury and osteoarthritis outcome score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64.
35 Frobell RB, Roos EM, Roos HP, *et al*. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med* 2010;363:331–42.
36 Roos EM, Grønne DT, Skou ST, *et al*. Immediate outcomes following the GLA:D® program in Denmark, Canada and Australia. A longitudinal analysis including 28,370 patients with symptomatic knee or hip osteoarthritis. *Osteoarthritis Cartilage* 2021;29:502–6.