Original Investigation

Evaluation of the Benefit of Corticosteroid Injection Before Exercise Therapy in Patients With Osteoarthritis of the Knee
A Randomized Clinical Trial

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IMPORTANCE Osteoarthritis (OA) of the knee is the most frequent form of arthritis and a cause of pain and disability. Combined nonpharmacologic and pharmacologic treatments are recommended as the optimal treatment approach, but no evidence supports the recommendation.

OBJECTIVE To assess the clinical benefits of an intra-articular corticosteroid injection given before exercise therapy in patients with OA of the knee.

DESIGN, SETTING, AND PARTICIPANTS We performed a randomized, blinded, placebo-controlled clinical trial evaluating the benefit of intra-articular corticosteroid injection vs placebo injection given before exercise therapy at an OA outpatient clinic from October 1, 2012, through April 2, 2014. The participants had radiographic confirmation of clinical OA of the knee, clinical signs of localized inflammation in the knee, and knee pain during walking (score >4 on a scale of 0 to 10).

INTERVENTIONS Participants were randomly allocated (1:1) to an intra-articular 1-mL injection of the knee with methylprednisolone acetate (Depo-Medrol), 40 mg/mL, dissolved in 4 mL of lidocaine hydrochloride (10 mg/mL) (corticosteroid group) or a 1-mL isotonic saline injection mixed with 4 mL of lidocaine hydrochloride (10 mg/mL) (placebo group). Two weeks after the injections, all participants started a 12-week supervised exercise program.

MAIN OUTCOMES AND MEASURES The primary outcome was change in the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (range, 0-100; higher scores indicate greater improvement) at week 14. Secondary outcomes included the remaining KOOS subscales and objective measures of physical function and inflammation. Outcomes were measured at baseline, week 2 (exercise start), week 14 (exercise stop), and week 26 (follow-up).

RESULTS One hundred patients were randomized to the corticosteroid group (n = 50) or the placebo group (n = 50); 45 and 44 patients, respectively, completed the trial. The mean (SE) changes in the KOOS Pain subscale score at week 14 were 13.6 (1.8) and 14.8 (1.8) points in the corticosteroid and placebo groups, respectively, corresponding to a statistically insignificant mean difference of 1.2 points (95% CI, −3.8 to 6.2; P = .64). We found no statistically significant group differences in any of the secondary outcomes at any time point.

CONCLUSIONS AND RELEVANCE No additional benefit results from adding an intra-articular injection of 40 mg of corticosteroid before exercise in patients with painful OA of the knee. Further research is needed to establish optimal and potentially synergistic combinations of conservative treatments.

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Osteoarthritis (OA) of the knee is common and associated with significant pain and disability.[1] Management aims to improve pain, function, and quality of life with first-line nonpharmacologic interventions, then adding of drugs, and ultimately surgery.[2]

Exercise is highly recommended for OA of the knee[3-5] and has been shown repeatedly to provide benefits for pain and physical function.[6-9] Pharmacologic treatments mainly target pain and inflammation, for which intra-articular injection of corticosteroids is recommended.[3,5,7,10] A combination of nonpharmacologic and pharmacologic treatment modalities are recommended for optimal nonsurgical management of OA of the knee.[2,10] However, only single treatments have been investigated, and assessment of whether combination therapy will provide synergistic clinical benefit is needed.[11,12]

Anti-inflammatory treatment before an exercise program may enhance the effects of exercise. Signs of inflammation, such as pain and effusion, significantly interfere with normal muscle recruitment and other motor functions.[13-15] Thus, through anti-inflammatory effects, intra-articular corticosteroid injections may provide a window of opportunity in which exercise can be delivered with greater clinical effects.

The purpose of this study was to assess the clinical efficacy of intra-articular corticosteroid injection given before an exercise program in patients with OA of the knee. We hypothesized that the combination of corticosteroid injection and exercise therapy would be superior to a combination of placebo injection and exercise therapy.

Methods

We performed a participant-, practitioner-, and outcome assessor-blinded, 2-arm, parallel-group, randomized, placebo-controlled clinical trial for 26 weeks from October 1, 2012, to April 2, 2014. The protocol was submitted to and approved by the Danish Health and Medicines Authority and the Regional Health Research Ethics Committee and was registered with the EU clinical trials database before commencement of the trial. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practices. The full study protocol can be found in the trial protocol in Supplement 1. All participants gave their oral and written informed consent. After initiating the trial, we made a second protocol registration at clinicaltrials.gov to emphasize which of the secondary outcomes we considered to be more important to this article.[16]

Setting and Eligibility Criteria

We recruited participants from the OA outpatient clinic at Copenhagen University Hospital at Bispebjerg and Frederiksberg, Copenhagen, Denmark. Inclusion criteria consisted of being 40 years or older and having a radiographic confirmation of a clinical diagnosis of tibiofemoral OA,[17] clinical signs of localized knee inflammation, knee pain during walking (score of >4 on a scale of 0-10 points), and a body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or less. Exclusion criteria included corticosteroid injections or participation in exercise therapy within the past 3 months, current or recent (within 4 weeks) use of oral corticosteroids, inflammatory arthritis, history of arthroplasty of the knee, conditions precluding participation in exercise, contraindications to corticosteroid injections, regional pain syndromes (eg, fibromyalgia), and spinal nerve root compression syndromes.

Procedures

Interested individuals underwent a telephone screening. Potentially eligible participants received written study information and were invited to a clinical screening examination by a rheumatologist with a special interest in OA (H.B.). During the examination, eligibility criteria were assessed, including a standardized, semiflexed, weight-bearing posterior-anterior knee radiograph, from which the diagnosis was confirmed by a trained radiologist.

The participants chose the most symptomatic knee as the target knee for all subsequent assessments, after which baseline measurements were performed. Subsequently, participants were randomized and the injections were performed. The exercise program commenced 2 weeks after the injection to allow expected maximal effect of the corticosteroid[18] and lasted for 12 weeks. All participants attended the same exercise classes. Outcomes were measured at baseline (before randomization), at the start of the exercise program (week 2; questionnaires only), after the exercise program (week 14), and after 12 weeks of follow-up (week 26).

Interventions

Participants in the corticosteroid group received a 1-mL intra-articular injection of methylprednisolone acetate (Depo-Medrol), 40 mg, dissolved in 4 mL of lidocaine hydrochloride (10 mg/mL). The placebo group received a 1-mL injection of isotonic saline mixed with 4 mL of lidocaine hydrochloride (10 mg/mL).

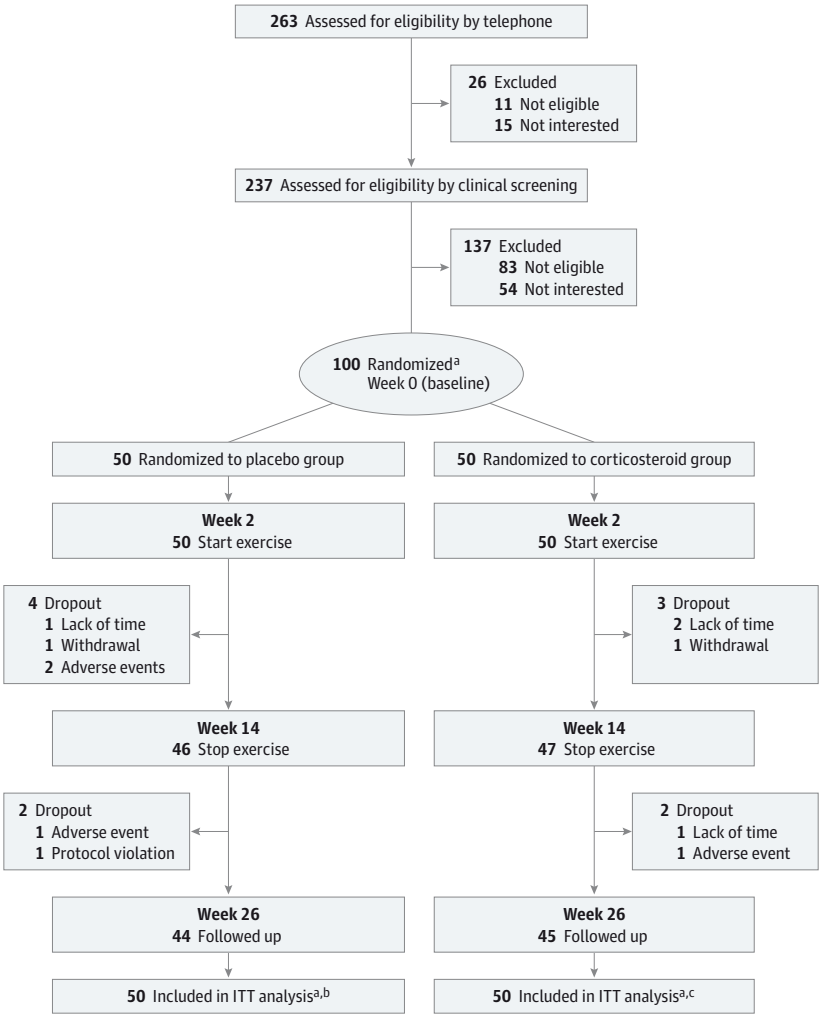
The injections were performed with a 25-gauge (38-mm) needle and a 10-mL syringe. A specialist in musculoskeletal sonography performed the injections under ultrasonographic guidance to ensure correct bolus deposition in the joint cavity. If present, excess joint fluid was aspirated before injection. The participants were informed that symptomatic exacerbation might occur during the following 48 hours.

The exercise program has been used in a previous trial,[19] and the details of the program have been described. In brief, the exercise program is functional and individualized and is supervised by a physiotherapist (C.B.) 3 times per week for 12 weeks. The program complies with minimal recommendations for inducing improvements relevant to OA of the knee.[9] The exercise was group based, with participants joining the group consecutively as they were included. Attendance at the exercise sessions was recorded.

Randomization, Treatment Allocation, and Blinding

After baseline measurements, the participants were randomized to intra-articular corticosteroid or placebo injection. A computer-generated randomization sequence was produced be-

Figure 1. CONSORT Diagram Showing Patient Flow Through the Trial



[a] Indicates intention-to-treat (ITT) population. Modified ITT population includes 95 participants who underwent contrast-enhanced magnetic resonance imaging (MRI).

[b] Modified ITT population includes 48 participants who underwent contrast-enhanced MRI.

[c] Modified ITT population includes 47 participants who underwent contrast-enhanced MRI.

fore any patients were enrolled that allocated participants in permuted blocks of 2 to 6 to the corticosteroid or the placebo group (1:1). The randomization sequence was prepared by a biostatistician with no clinical involvement in the trial (R.C.). The allocation was concealed in a password-protected computer file only accessible by the biostatistician. Individual allocations were held in sealed, opaque, consecutively numbered envelopes.

Envelopes were opened sequentially by a nonblinded study nurse. To ensure blinding of the participants and the clinician performing the injections, the syringes were prepared by the study nurse in the absence of participants and blinded study staff. Because the corticosteroid liquid is milky white and the saline is clear, the syringes were masked with opaque tape to prevent disclosure of the content during the injection procedure. This procedure ensured that participants, study staff, and outcomes assessors were blinded to treatment allocations throughout the trial.

Outcome Measures

Outcomes were measured at baseline, at the 2- and 14-week visits (the latter was the primary end point), and at the 26-week follow-up visit (12 weeks after the exercise program). Because we expected maximal clinical effects of the combined intervention on pain after 14 weeks, the primary outcome was chosen as the change from baseline to the week 14 visit in the Pain subscale of the patient-reported Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire.[20] The remaining 4 KOOS subscales (Symptoms, Function in Daily Living, Function in Sport and Recreation, and Knee-Related Quality of Life) were considered secondary outcomes. Other important secondary outcome measures were changes from baseline in a functional weight-bearing pain test, muscle strength,[21] 6-minute walking distance,[22] plasma concentration of interleukin 6 measured from fasting morning blood samples, and semiquantitative assessments of effusion and synovitis before and after contrast-enhanced magnetic resonance imaging (MRI).[23] Detailed descriptions of the outcome measures are in the eMethods in Supplement 2.

Only participants without contraindications underwent MRI. The contrast agent was only administered to participants with an estimated glomerular filtration rate of greater than 60 mL/min/1.73 m^2 owing to the potential nephrogenic

Table 1. Baseline Characteristics and Values for Primary and Secondary Outcomes

Characteristic	Intervention Arm[a]		All Participants (N = 100)
	Placebo (n = 50)	Corticosteroid (n = 50)	
Demographic Characteristic			
Female sex, No. (%)	33 (66)	28 (56)	61 (61)
Age, y	65.5 (8.3)	61.3 (9.9)	63.4 (9.3)
Height, m	1.69 (0.09)	1.73 (0.10)	1.71 (0.10)
Weight, kg	82.8 (11.4)	86.5 (14.8)	84.6 (13.2)
BMI	28.9 (3.3)	29.0 (3.9)	28.9 (3.6)
Radiographic Severity			
Grade, No. (%)[b]			
1	0	4 (8)	4 (4)
2	18 (36)	21 (42)	39 (39)
3	17 (34)	15 (30)	32 (32)
4	15 (30)	10 (20)	25 (25)
Primary Outcome			
KOOS Pain subscale score[c]	55.2 (16.0)	53.3 (11.4)	54.3 (13.9)
Secondary Outcomes			
KOOS subscale score[c]			
Symptoms	56.8 (19.3)	59.0 (15.2)	57.9 (17.3)
Function in Daily Living	62.6 (18.6)	61.0 (14.7)	61.8 (16.7)
Knee-Related Quality of Life	39.0 (14.4)	36.8 (12.7)	37.9 (13.6)
Function in Sports and Recreation	28.7 (19.8)	29.6 (17.7)	29.2 (18.7)
Functional weight-bearing pain			
No. of squats in 30 s	15.1 (5.6)	17.7 (7.1)	16.4 (6.5)
No. of pain-free squats	3.2 (7.3)	1.8 (6.1)	2.5 (6.7)
Pain intensity during squats[d]	3.6 (2.3)	4.1 (2.1)	3.8 (2.2)
Muscle Strength			
Quadriceps, Nm/kg			
0°/s	114.8 (46.6)	132.9 (53.2)	123.9 (50.6)
60°/s	83.5 (35.3)	106.2 (46.7)	94.9 (42.7)
120°/s	74.5 (30.3)	94.0 (41.2)	84.2 (37.3)
180°/s	65.1 (25.4)	81.8 (35.3)	73.5 (31.7)
Hamstrings, Nm/kg			
0°/s	59.0 (25.9)	71.7 (31.2)	65.4 (29.2)
60°/s	45.4 (21.7)	57.3 (26.8)	51.3 (25.0)
120°/s	38.8 (18.0)	55.1 (23.4)	47.0 (22.3)
180°/s	36.8 (16.3)	48.8 (22.6)	42.8 (20.5)
6-min Walk distance, m	494.8 (84.9)	555.5 (99.8)	525.1 (97.1)
Blood Sample Analysis			
Plasma concentration of IL-6, pg/mL	11.4 (12.9)	8.8 (6.5)	10.1 (10.2)
MRI Analysis			
No. undergoing MRI[e]	48	47	95
Effusion synovitis score[f]	2.2 (0.6)	1.9 (0.7)	2.0 (0.7)
Score, No. (%)			
0	0	0 (0)	0 (0)
1	6 (13)	15 (32)	21 (22)
2	27 (56)	24 (51)	51 (54)
3	15 (31)	8 (17)	23 (24)
Hoffa synovitis score[f]	2.5 (0.6)	2.5 (0.7)	2.5 (0.7)
Score, No. (%)			
0	0 (0)	1 (2)	1 (1)
1	3 (6)	4 (9)	7 (7)
2	16 (33)	13 (28)	29 (31)
3	29 (60)	29 (62)	58 (61)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IL-6, interleukin 6; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; Nm, newton meter.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Calculated on the Kellgren-Lawrence scale (range, 0-4), with 0 indicating no osteoarthritic changes.

[c] Scores range from 0 to 100, with higher scores indicating better outcomes.

[d] Scores range from 0 to 10, with higher scores indicating more pain.

[e] Data were not available for all randomized participants defining the modified intention-to-treat population.

[f] Scores range from 0 to 3, with higher scores indicating more effusion/synovitis.

adverse effects.[24] An estimated glomerular filtration rate of less than 60 was not a criterion for trial exclusion; that is, we accepted that not all participants underwent contrast-enhanced MRI at every time point. Baseline radiographs were read in a batch by a trained radiologist (M.P.B.), and radiographic OA severity was graded using the Kellgren-Lawrence

scale.[25] All data acquisition, processing, and analyses, including radiograph readings, physical performance test results, and MRI readings, were performed by study staff who were blinded to group allocation.

Sample Size

The study was powered for a comparison between the participants allocated to corticosteroid and those allocated to placebo. Assuming that the corticosteroid condition would produce a reduction in the KOOS Pain subscale that was 10 points larger than that of the placebo condition, with an SD of 15 points, we calculated that we would need 100 patients in the intention-to-treat (ITT) population to test a 2-tailed hypothesis with 91% power at a 5% level of statistical significance.

Statistical Analysis

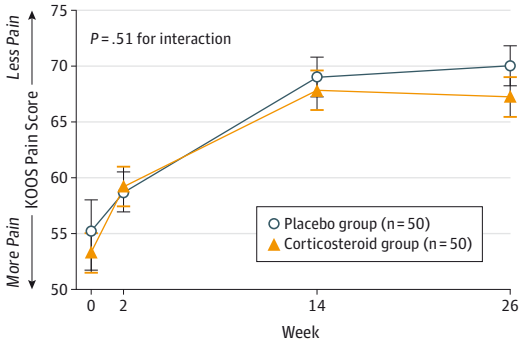
Statistical analyses were performed on the ITT population, including all randomized participants. Missing data were replaced using multiple imputation (5 iterations), including age, sex, body mass index, baseline scores, and group allocations (blinded) as predictors. A modified ITT population was used in the analysis of contrast-enhanced MRI data.

We analyzed continuous outcomes using repeated-measures mixed linear models, including participants as a random effect, with fixed factors for group (2 levels) and week (3 levels for the KOOS questionnaire [weeks 2, 14, and 26] and 2 levels for other outcomes [weeks 14 and 26]) and the corresponding interactions, adjusted for baseline values. To assess the adequacy of the linear models describing the observed data—and checking assumptions for the systematic and the random parts of the models—we investigated the model features via the predicted values and the residuals; that is, the residuals had to be normally distributed (around 0) and be independent of the predicted values. Results are expressed as estimates of the group differences in the changes from baseline, with 95% CIs to represent precision of the estimates.

Semiquantitative MRI assessments of effusion synovitis and Hoffa synovitis were also analyzed as binary outcomes after dichotomization into improvement (ie, a reduction from the baseline score of at least 1) or no response. The dichotomized outcomes were analyzed using repeated-measures generalized linear mixed models with a factor for group (2 levels) and a factor for week (2 levels [weeks 14 and 26]) and the corresponding interaction, adjusted for the baseline grade. Results are expressed as the number of patients with improvement and odds ratios for improvement in the corticosteroid group relative to the placebo group with 95% CIs.

Sensitivity analyses were performed on the ITT population using a baseline observation carried forward imputation technique and on the available case population (no imputation). All statistical analyses were performed on blinded group allocations. Unblinding was performed after completion of all the prespecified statistical analyses. We set the statistical significance at the conventional level of .05. All analyses were performed using commercially available statistical software (SAS, version 9.3; SAS Institute Inc).

Figure 2. Group Patterns of Self-reported Pain



Pain was assessed by the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (score range, 0-100). The graph illustrates the results from the intention-to-treat analysis in which all patients were included. Thus, there were 100 patients at each time point (ie, 50 in each group). High values represent less pain; low values, more pain. Data points represent means; error bars, SE.

Results

Of 263 individuals screened by telephone, 237 attended the clinical screening. Of these, 100 participants were randomized and constituted the ITT population (**Figure 1**). At baseline, 5 participants (2 in the placebo group and 3 in the corticosteroid group) did not undergo contrast-enhanced MRI owing to contraindications; thus, the modified ITT population consisted of 95 participants. The groups were balanced at baseline (**Table 1**). Eighty-nine participants completed the week 26 follow-up (Figure 1), with no group differences. Eighteen participants (8 in the corticosteroid group and 10 in the placebo group) underwent aspiration of excess joint fluid at randomization. Of these, 10 participants (6 in the corticosteroid group and 4 in the placebo group) underwent aspiration at week 14, and 7 participants (6 in the corticosteroid group and 1 in the placebo group) underwent aspiration at week 26. The participants attended a mean of 28 of 36 sessions (78%) in the corticosteroid group and 29 of 36 sessions (81%) in the placebo group.

Primary Outcome

The KOOS Pain subscale outcomes at weeks 2, 14, and 26 are illustrated in **Figure 2**. Results of the primary outcome measure at week 14 are presented in **Table 2**. At the primary end point (week 14), the group difference in the change from baseline in Pain subscale score was 1.2 KOOS points (95% CI, −3.8 to 6.2 [P = .64]). The results were robust to sensitivity analyses (eTables 1 and 2 in Supplement 2).

Secondary Outcomes

Changes from baseline in the secondary outcomes at week 14 are presented in Table 2 showing no statistically significant group differences. The week 2 outcomes are presented in **Table 3** (KOOS questionnaire only), with no statistically significant group differences. Changes from baseline in all outcomes at week 26 are presented in eTable 3 in Supplement 2, showing

Table 2. Comparison of Changes in Primary and Secondary Outcomes at the Main Trial End Point[a]

Change From Baseline at Week 14	Intervention Arm		Comparison	
	Placebo (n = 50)	Corticosteroid (n = 50)	Mean Difference (95% CI)	*P* Value[b]
Primary Outcome				
KOOS Pain subscale score[c]	14.8 (1.8)	13.6 (1.8)	1.2 (−3.8 to 6.2)	.64
Secondary Outcomes				
KOOS subscale scores[c]				
Symptoms	12.1 (1.8)	13.3 (1.8)	−1.2 (−6.1 to 3.7)	.63
Function in Daily Living	15.0 (1.7)	14.9 (1.7)	0.1 (−4.6 to 4.8)	.96
Knee-Related Quality of Life	8.4 (1.8)	9.3 (1.8)	−0.9 (−5.9 to 4.1)	.72
Function in Sports and Recreation	15.5 (2.4)	16.8 (2.4)	−1.3 (−8.0 to 5.4)	.70
Functional weight-bearing pain				
No. of squats in 30 s	9.0 (1.4)	6.6 (1.4)	2.4 (−1.5 to 6.2)	.23
No. of pain-free squats	10.8 (2.0)	7.7 (2.0)	3.1 (−2.4 to 8.6)	.27
Pain intensity during squats[d]	−2.3 (0.3)	−2.1 (0.3)	−0.2 (−1.0 to 0.6)	.57
Muscle Strength				
Quadriceps, Nm/kg				
0°/s	7.7 (3.2)	9.9 (3.2)	−2.1 (−11.0 to 6.7)	.63
60°/s	5.0 (2.7)	3.1 (2.7)	2.0 (−5.8 to 9.8)	.62
120°/s	1.2 (2.1)	2.0 (2.1)	−0.8 (−6.7 to 5.1)	.79
180°/s	1.2 (1.8)	1.8 (1.8)	−0.6 (−5.6 to 4.4)	.82
Hamstrings, Nm/kg				
0°/s	3.2 (2.5)	9.2 (2.5)	−6.1 (−13.1 to 1.0)	.09
60°/s	4.7 (2.1)	8.0 (2.1)	−3.3 (−9.2 to 2.5)	.26
120°/s	2.9 (2.1)	2.3 (2.1)	0.5 (−5.5 to 6.6)	.86
180°/s	4.0 (1.5)	4.8 (1.5)	−0.9 (−5.1 to 3.3)	.69
6-min Walk distance, m	19.9 (7.3)	20.7 (7.3)	−0.8 (−21.7 to 20.1)	.94
Blood Sample Analysis				
Plasma concentration of IL-6, pg/mL	−1.10 (0.87)	−0.92 (−2.64)	−0.18 (−2.62 to 2.25)	.88
MRI Analysis				
MRI (continuous)[e]	48	47	NA	NA
Effusion synovitis score[f]	−0.2 (0.1)	−0.3 (0.1)	0.1 (−0.2 to 0.4)	.54
Hoffa synovitis score[f]	−0.2 (0.1)	−0.3 (0.1)	0.1 (−0.3 to 0.5)	.62
MRI (binary)[e]	48	47	NA	NA
No. (%) of participants				
Effusion synovitis improved	6 (13)	12 (26)	2.30 (0.80 to 7.01)[g]	.14
Hoffa synovitis improved	4 (8)	7 (15)	1.89 (0.50 to 7.16)[g]	.35

Abbreviations: IL-6, interleukin 6; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; NA, not applicable; Nm, newton meter.

[a] Indicates 14 weeks after randomization after completion of the exercise therapy. Unless otherwise indicated, data are reported as mean (SE).

[b] Analyzed by contrasting groups using repeated-measures mixed linear models.

[c] Scores range from 0 to 100, with higher scores indicating better outcomes.

[d] Scores range from 0 to 10, with higher scores indicating more pain.

[e] Indicates modified intention-to-treat population.

[f] Scores range from 0 to 3, with higher scores indicating more effusion/synovitis.

[g] Data reported as odds ratio (95% CI).

Table 3. Comparison of Self-reported Questionnaire Data at the Week 2 Assessment[a]

Change From Baseline at Week 2	Intervention, Mean (SE)		Comparison	
	Placebo (n = 50)	Corticosteroid (n = 50)	Mean Difference (95% CI)	*P* Value[b]
Primary Outcome				
KOOS Pain subscale score[c]	4.5 (1.8)	5.0 (1.8)	−0.5 (−5.5 to 4.5)	.85
Secondary Outcomes				
KOOS subscale scores[c]				
Symptoms	4.3 (1.8)	4.6 (1.8)	−0.3 (−5.2 to 4.6)	.91
Function in Daily Living	5.1 (1.7)	4.0 (1.7)	1.2 (−3.5 to 5.9)	.63
Knee-Related Quality of Life	4.0 (1.8)	4.2 (1.8)	−0.2 (−5.2 to 4.8)	.94
Function in Sports and Recreation	2.7 (2.4)	5.8 (2.4)	−3.1 (−9.8 to 3.6)	.36

Abbreviation: KOOS, Knee Injury and Osteoarthritis Outcome score.

[a] Indicates start of exercise program.

[b] Analyzed by contrasting groups using repeated-measures mixed linear models.

[c] Scores range from 0 to 100, with higher scores indicating better outcomes.

no statistically significant group differences except isometric hamstring muscle strength (favoring the corticosteroid condition) and the MRI outcomes (favoring the placebo condition). These significant findings were not robust to the sensitivity analyses, which confirmed the lack of group differences across all outcomes and time points (eTables 1 and 2 in Supplement 2).

Ancillary Analyses

We repeated the analyses on a selected modified ITT subpopulation with signs of high baseline inflammation (MRI effusion synovitis score, ≥2). This subgroup consisted of 74 participants (32 in the corticosteroid group and 42 in the placebo group, including the 18 participants who underwent joint fluid aspiration at baseline). The results confirmed the primary analyses (eTable 4 in Supplement 2).

Discussion

This study was designed to rigorously evaluate the clinical efficacy of 1 intra-articular corticosteroid injection given before an exercise program for treating knee pain in OA. This study is, to our knowledge, the first to assess the combined effects of intra-articular corticosteroid and exercise—2 recommended conservative management modalities—on important knee OA outcomes. The study found no benefit of the corticosteroid treatment compared with placebo when combined with exercise.

Although considerable improvements were observed at every time point, no differences between the corticosteroid and placebo groups were found. This finding contrasts with previous studies on corticosteroid treatment[18,26] showing beneficial short-term (ie, 2 weeks) effects of the corticosteroid compared with placebo. The considerable amount of attention given to all of the participants and the participants' expectations concerning the upcoming exercise program may have overshadowed the effect of corticosteroid treatment. The lack of additional effect of the corticosteroid compared with saline and lidocaine at week 2 is all the more noticeable because the participants had definite signs of inflammation in the knees on MRI at baseline. Ancillary analyses focusing on the participants with a high baseline degree of inflammation (including those who underwent aspiration of joint fluid) confirmed the main analyses, suggesting lack of effect even in individuals with definite clinical signs of inflammation.

The dose of corticosteroid used is in the lower range of the recommended dosage for knee joints, and the lack of additional effect of corticosteroid injection compared with saline and lidocaine makes it unlikely that a low-dose intra-articular corticosteroid injection would augment the beneficial effects of exercise, as otherwise hypothesized. Although the dose-response relationship is unknown, the low dose may be a limitation of this study, and a higher dose may show different results. Another possible limitation is the addition of lidocaine to the injection. This formulation is the current standard at our institution and is applied in an attempt to prevent possible symptomatic flare-up associated with corticosteroid injection. Because lidocaine was given to both groups, valid comparisons of corticosteroid and placebo are allowed, and the parallel pain improvements in both groups at week 2 may be attributable to the lidocaine.

The inventors of the KOOS questionnaire suggest a minimal important difference of 8 to 10 points (http://www.koos.nu), which corresponds with the practical equivalence margins used previously.[27] Accordingly, we powered our study for detection of a 10-point group difference, but no difference was detected. Our 95% CI respects this pragmatic equivalence margin and suggests comparable efficacy of corticosteroid treatment and placebo given before exercise. Minimal important differences for OA of the knee have not been established for the secondary outcomes. All in all, our results indicate comparable if not equivalent efficacy; nevertheless, because this study was designed for superiority, equivalence must be confirmed in an equivalence study.[28]

Our findings should be considered in therapeutic decision making. Intra-articular corticosteroid injection and exercise are highlighted in recommendations and guidelines.[3-5,7,29] However, our results do not support the superiority of intra-articular injection of corticosteroid compared with saline and lidocaine before an exercise intervention.

Conclusions

Our results suggest no additional clinical benefit by adding 40 mg of methylprednisolone acetate (Depo-Medrol) to an intra-articular injection of saline and lidocaine before exercise in patients with OA of the knee. Further research is needed to establish optimal and potentially synergistic combinations of conservative treatments of OA of the knee.

ARTICLE INFORMATION

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Study concept and design: Henriksen, Christensen, Bliddal.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Henriksen, Christensen, Bliddal.
Critical revision of the manuscript for important intellectual content: All authors.
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Study supervision: Henriksen, Bliddal.

Conflict of Interest Disclosures: Dr Henriksen is associated with the Danish Association of Physiotherapists, which could benefit from wide uptake of this publication. Dr Christensen is involved in many health care initiatives and research that could benefit from wide uptake of this publication (including Cochrane, Outcome Measures in Rheumatology [OMERACT], and the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] Working Group). No other disclosures were reported.

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acquisition of the radiographs and magnetic resonance images. The laboratory technicians Eva Andersen, BSc, Jack Olsen, BSc, and Inger Wætjen, BSc, from the Parker Institute obtained and analyzed blood samples. Study nurses Merete Wille, RN, Christine Tara Lang, RN, and Lizzie Zafirakos, RN, at the Parker Institute managed the study drugs and cared for participants during the study visits. Physical therapists Katrine Mouritsen, BSc, and Helene Clausen, BSc, at the Parker Institute assisted in providing the exercise intervention. None of these contributors received additional compensation beyond their usual salaries for their contributions.

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