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Changes in ultrasound assessed markers of inflammation following intra-articular steroid injection combined with exercise in knee osteoarthritis: exploratory outcome from a randomized trial

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SUMMARY

Objective: Knee osteoarthritis (KOA) is a multifactorial joint disease affecting many people worldwide. Recommended treatments for KOA include exercise and steroid injections, or a combination of these. The objective of this exploratory outcome analysis of a randomized trial was to assess changes in inflammation markers assessed by ultrasound imaging (US) in KOA secondary to intra-articular corticosteroid injection given prior to exercise therapy.
Design: This study is a sub-study to a larger clinical trial which compared the clinical effects of steroid injection in KOA to placebo injection, both given prior to exercise therapy. The US outcomes were changes from baseline in US-assessed synovial size, Doppler activity presence in the synovial membrane, and numbers of US-detected Baker's cysts. US was performed at baseline, week 14 (exercise stop), and week 26 (follow-up).
Results: Fifty participants received steroid injection, and 50 received placebo injection. All participants received 12 weeks of exercise. Forty-five and 44, respectively, completed the study. At week 14, the group difference in the change in synovium thickness was 2.2 mm (95%, confidence interval (CI) −0.5 to 4.8), $P = 0.11$. There were no group differences in the changes in distribution of patients with presence of synovial Doppler activity ($P = 0.98$) or Baker's cysts ($P = 0.35$). There were no statistically significant differences between groups at week 26 in any outcome.
Conclusion: Intra-articular steroid injection of KOA-patients prior to a 3 months exercise programme did not reduce synovial hypertrophy, synovial Doppler activity, or Baker's cyst presence more than a placebo saline injection according to US-assessments.
Trial registration: EudraCT: 2012-002607-18.

Introduction

Knee osteoarthritis (KOA) is a common joint disease and the global prevalence is approximately 4%[1]. KOA is a complex multifactorial joint disease characterized by articular cartilage loss, local inflammation, and remodelling of subchondral bone.

KOA is diagnosed according to The American College of Rheumatology (ACR) including clinical variables such as knee pain, age, morning stiffness, crepitus, bone enlargement and bone tenderness[2]. Radiographic KOA is often graded by the Kellgren and Lawrence (K&L) score with grades 0–4, according to joint space narrowing and structural changes in the bone[3].

According to guidelines from The Osteoarthritis Research Society International (OARSI), non-surgical treatment of KOA should be first choice and may include both physical exercise and intra-articular corticosteroid injections[4]. It is believed that the therapeutic effect of corticosteroids in KOA is anti-inflammatory.

Ultrasound imaging (US) is a non-invasive procedure that can be used to assess inflammatory markers related to the synovial membrane and Baker's cysts[5,6]. Grey scale US images visualise structural changes such as synovial hypertrophy and fluid, and

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adding Doppler US to the grey scale image will add information of movements of erythrocytes in the capillary network in e.g., the synovial membrane. US Doppler can therefore be used as an indirect measure of increased tissue perfusion.

This study is a sub-study of a larger randomized double-blinded, placebo-controlled clinical trial[7] aiming at investigating the effect of intra-articular steroid injection therapy given 2 weeks prior to a 12-week exercise program in individuals with KOA. The clinical results suggested comparable effects of steroid and placebo given prior to exercise, yet it remains unknown if the combination yields beneficial effects on US-assessed signs of knee joint inflammation.

The aim of the present study was to investigate if US-assessed markers of inflammation (synovial hypertrophy, Doppler activity, and Baker's cyst presence) are affected by intra-articular steroid therapy combined with exercise therapy.

Methods

The main clinical trial was a participant-, care provider-, outcome assessor blind, two-arm, parallel-group, randomized, and placebo-controlled trial, running over 26 weeks from October 2012 to April 2014 with patient-reported pain as primary outcome. The results of the primary and key secondary outcomes of the trial can be found elsewhere[7]. The protocol (available from corresponding author) was submitted to and approved by the Danish Health and Medicines Authority and the Regional Health Research Ethics Committee, and was registered with the mandatory European Union (EU) clinical trials register (EudraCT number: 2012-002607-18) prior to commencement of the trial. The trial was conducted in accordance with the Helsinki Declaration and ICH GCP.

Setting and eligibility criteria

Participants were recruited from the osteoarthritis outpatient clinic at Copenhagen University Hospital at Bispebjerg and Frederiksberg, Denmark. Inclusion criteria were age 40 years or above, a radiographically confirmed clinical diagnosis of tibiofemoral OA (ACR criteria), clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index $\leq$ 35 kg/m^2. Exclusion criteria included corticosteroid injections or participation in exercise therapy within 3 months, current or recent (within 4 weeks) use of oral corticosteroids, inflammatory arthritis, history of knee arthroplasty or osteotomy, other conditions precluding participation in exercise, contraindications to corticosteroid injections, regional pain syndromes such as fibromyalgia, and lumbar or cervical nerve root compression syndromes.

Procedures

All participants gave their oral and written informed consent after screening and having the eligibility criteria assessed, including a bilateral, standardized, semi-flexed weight-bearing posterior–anterior knee radiograph used to radiographically confirmation of the diagnosis (interpreted by a trained radiologist). The participants chose the most symptomatic knee as target knee for injection and all subsequent assessments, including US examination. Upon complete baseline assessments participants were randomized and the injection was performed. The exercise program was commenced 2 weeks after the baseline date and lasted for 12 weeks. All participants attended the same exercise classes.

Randomization, treatment allocation, and blinding

Following the baseline measurements, the participants were randomized equally (1:1) to either intra-articular corticosteroid or placebo injection. The pre-specified allocation list was concealed in a password protected computer file. Individual allocations were held in sealed, opaque, and consecutively numbered envelopes. Details can be found elsewhere[7].

To ensure blinding of the participants, investigators, outcome assessors, and the person carrying out the injections throughout the trial, the syringes were prepared by the un-blinded 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 by opaque tape to prevent disclosure of the content during the injection procedure.

Interventions

Participants in the corticosteroid group received an intra-articular injection with 1 mL methylprednisolone (40 mg Depo-Medrol®, Pfizer) dissolved in 4 mL lidocaine (10 mg/mL, SAD), and participants in the placebo group received an injection with 1 mL isotonic saline mixed with 4 mL lidocaine (10 mg/mL, SAD).

The injections were carried out with a 25 gauge (38 mm) needle and a 10 mL Luer-lock syringe. An experienced specialist in musculoskeletal sonography performed the injections under ultrasound guidance ensuring correct bolus deposition in the joint cavity. If present, excess joint fluid was aspirated prior to injection.

The exercise program has been applied previously, and details can be found elsewhere[7,8]. In brief, the exercise program was a facility-based, functional and individualized exercise program supervised by a trained physiotherapist three times weekly for 12 weeks.

Outcome measures

Outcomes were measured at baseline (2 weeks before randomization and injection), at week 14 (immediately after the 12-week exercise program), and at the 26 weeks follow-up visit (12 weeks after the exercise program).

For the purpose of this exploratory US study outcome analyses, we examined changes from baseline in the thickness of the synovial membrane, synovial Doppler activity presence, and presence of Baker's cysts at weeks 14 and 26.

US examination

All US examinations were carried out using a General Electric E9 scanner, with a 15 MHz linear array transducer (General Electrics Medical System, Milwaukee, WI, USA) with image acquisition settings unchanged throughout the study period. The gain setting for the colour Doppler was just below noise level and the system was adjusted to maximum sensitivity for any flow (pulse repetition frequency 3 Hz, lowest wall filter, and 6.3 MHz Doppler frequency)[9]. Two investigators performed the US examinations which were carried out according to a standardized protocol. Both US examiners had many years of experience in musculoskeletal US (10 and 20 years, respectively).

The positions examined were based on recommendations in the literature on US examination of patients with KOA[10–12]. Furthermore, the chosen scanning positions displayed good reliability in patients with KOA[13]. The positions examined were: the suprapatellar recess (landmark: patella and femoral bone); the medial and lateral joint space (landmark: femoral and tibial bone); medial and lateral recess (landmark: femoral bone). All anterior scans were