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The effects of intra-articular glucocorticoids and exercise on pain and synovitis assessed on static and dynamic magnetic resonance imaging in knee osteoarthritis: exploratory outcomes from a randomized controlled trial

R.G.C. Riis † ‡ §, M. Henriksen † ||, L. Klokker †, C. Bartholdy † ||, K. Ellegaard †, E. Bandak †, B.B. Hansen †, H. Bliddal †, M. Boesen † ‡ *

† *The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark*
‡ *Dept. of Radiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark*
§ *Dept. of Radiology, Zealand University Hospital, Holbaek, Denmark*
|| *Dept. of Physical & Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark*

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SUMMARY

Objective: The aims of the present knee osteoarthritis (KOA)-study were to: (1) describe and compare the changes in magnetic resonance imaging (MRI)-measures of synovitis following an exercise program preceded by an intra-articular injection of either corticosteroid or isotonic saline and (2) investigate if any of the changes in patient reported outcome measures (PROMs) were associated with changes in MRI-measures of synovitis.

Design: We performed a randomized, double-blinded, placebo-controlled clinical trial evaluating the effects of intra-articular corticosteroid vs placebo injections given before exercise therapy in KOA-patients. PROMs were assessed using the KOOS (knee injury and osteoarthritis outcome score). Synovitis was assessed on conventional non-contrast-enhanced, conventional contrast-enhanced (CE) and dynamic contrast-enhanced (DCE) MRI. PROMs and MRIs were obtained prior to the intra-articular injection, after termination of the exercise program (week 14—primary time point) and week 26.

Results: Of 100 randomized participants (50 in each allocation group), 91 had complete MRI-data at baseline (63% female, mean age: 62 years, median Kellgren–Lawrence-grade: 3). There were no statistically significant differences between the two interventions in regards of changes in MRI-measures of synovitis at any time-point. At week 14, we found no statistical significant MRI-explanatory variables of either of the PROMs.

Conclusions: The present study does not justify the use of intra-articular corticosteroids over intra-articular saline when combined with an exercise program for reduction of synovitis in KOA. The improvement in pain and function following the intervention with intra-articular corticosteroids/saline and exercise could not be explained by a decrease in synovitis on MRI indicating other pain causing/relieving mechanisms in KOA.

Introduction

Synovitis is the hallmark of intra-articular inflammation and a common finding in all stages of knee osteoarthritis (OA)[1,2]. It is generally accepted that synovitis is associated with pain in knee OA[3,4]. Synovitis has also been associated with structural disease severity and cartilage loss in both established knee OA[3,5], in persons at risk of knee OA[6–8] as well as a risk factor for total knee arthroplasty (TKA)[7,9]. As a consequence hereof, synovitis is increasingly

* Address correspondence and reprint requests to: M. Boesen, Department of Radiology and the Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark. Fax: 45-3816-4159.
E-mail addresses: riis.robert@gmail.com (R.G.C. Riis), marius.henriksen@regionh.dk (M. Henriksen), louise.klokker.madsen@regionh.dk (L. Klokker), cecilie.roedgaard.bartholdy@regionh.dk (C. Bartholdy), karen.ellegaard@regionh.dk (K. Ellegaard), elisabeth.ann.bandak@regionh.dk (E. Bandak), dr.bjarke@gmail.com (B.B. Hansen), henning.bliddal@regionh.dk (H. Bliddal), mikael.boesen@regionh.dk, mikael.boesen@gmail.com (M. Boesen).

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being addressed as a treatment target in both pre-knee OA and established knee OA.

Synovitis can be assessed on magnetic resonance imaging (MRI), optimally on contrast-enhanced (CE)-MRI, as only this allows the discrimination of the synovium from a joint effusion[10,11]. When performing CE-MRI, a dynamic contrast-enhanced (DCE)-MRI sequence can be added.

In DCE-MRI, imaging is not only performed before and after but also *during* the intravenous (IV) injection of gadolinium (Gd). DCE-MRI data are typically analyzed using either a heuristic or pharmacokinetic approach. Heuristic analyses are based on the changes in signal intensity over time following Gd-injection (so-called time-intensity-curves, TICs). Pharmacokinetic analysis relies on converting TICs to concentration-time-curves (CTCs), i.e., changes in Gd-concentration over time; by fitting data from the CTCs with pharmacokinetic models, e.g., the extended Tofts model, pharmacokinetic parameters such as K^{trans}, a measure of capillary permeability, can be extracted.

As the distribution of Gd depends on the perfusion, DCE-MRI parameters can be used as surrogate markers of perfusion and DCE-MRI parameters from the synovium[12] and Hoffa's fat pad[13] have recently been shown to correlate with pain and function in knee OA. In addition, recent studies have shown that DCE-MRI variables are more sensitive to changes following treatment with intra-articular corticosteroid compared to measures of the synovial volume[14] and a semi-quantitative CE-MRI score[15] which also seems to be the case in rheumatoid arthritis (RA)[16].

Intra-articular corticosteroids have been used in knee OA for several decades. The therapeutic response is probably due to their anti-inflammatory effect and intra-articular corticosteroids as well as exercise are widely recommended in the non-surgical management of knee OA[17–21].

Our study is part of a randomized, double-blinded, placebo-controlled, clinical knee OA-trial in which no benefit of intra-articular corticosteroids compared to intra-articular saline administered prior to an exercise program could be detected, neither in regards of clinical outcomes[22,23], nor in regards of ultrasonography-assessed measures of knee joint inflammation[24]. It however remains unknown what the effects on MRI-measures of synovitis are. As synovitis seems to play a role in the development and progression of knee OA, interventions that reduce synovitis in the long term could have important clinical implications for the management of persons with or at risk of knee OA.

The aims of our study were to: (1) describe and compare the changes in MRI-measures of synovitis following an exercise program preceded by an intra-articular injection of either corticosteroid or isotonic saline, and (2) investigate if any of the changes in patient reported outcome measures (PROMs) were associated with changes in MRI-measures of synovitis. We hypothesized that (1) the combination of steroid and exercise was more effective in reducing synovitis assessed on MRI compared to isotonic saline and exercise, and (2) the improvement in PROMs was paralleled by a reduction in MRI-measures of synovitis.

Methods

The main clinical trial was a participant-, care provider-, outcome assessor blinded, 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[22]. The results of the primary and key secondary outcomes can be found elsewhere[22–24]. The protocol was registered with the EU clinical trials register (Eudra-CT number: 2012-002607-18) and was approved by the Danish Health and Medicines Authority and the Regional Health Research Ethics Committee. The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

Setting and eligibility criteria

Participants were recruited from the OA outpatient clinic, Copenhagen University Hospital, Bispebjerg-Frederiksberg, Denmark. Inclusion criteria included: age $\geq$ 40 years, radiographically verified diagnosis of tibiofemoral OA (American College of Rheumatology-criteria), clinical signs of localized knee inflammation, knee pain during walking (> 4 on a 0–10 point scale), and a body mass index (BMI) $\leq$ 35 kg/m^2. Exclusion criteria included: corticosteroid injections or participation in exercise therapy within 3 months, current/recent (within 4 weeks) use of oral corticosteroids, contraindications to corticosteroid injections, conditions precluding participation in exercise, inflammatory arthritis, history of knee arthroplasty or osteotomy, generalized pain syndromes (e.g., fibromyalgia) or local nerve root compression syndromes. Only participants without contraindications underwent MRI. The contrast agent was only administered to participants with an estimated glomerular filtration rate $\geq$ 60 ml/min/1.73 m^2. All participants gave their oral and written informed consent.

Procedures

The participants chose the most symptomatic knee as target knee for injection and all subsequent assessments. Upon complete baseline assessments, participants were randomized and the injection was performed. The exercise program commenced two weeks after the baseline assessments and lasted for 12 weeks. The exercise program was identical in both allocation groups.

Randomization, treatment allocation, and blinding

Participants were randomized equally (1:1) to an intra-articular injection of either corticosteroid or placebo. The pre-specified allocation list was concealed in a password-protected computer file. Individual allocations were held in sealed, opaque, and consecutively numbered envelopes. Syringes were prepared by an un-blinded study nurse in the absence of participants and blinded study staff. Details about the randomization, allocations and blinding can be found elsewhere[22].

Sample size

The hosting study was powered for a comparison in the pain subscale of the KOOS (knee injury and osteoarthritis outcome score) between the two allocation groups and included 100 individuals[22].

Interventions

Intra-articular injections were performed by an experienced musculoskeletal (MSK) sonographer (KE) under ultrasound (US) guidance ensuring correct bolus deposition in the joint cavity. If present, excess joint fluid was aspirated prior to injection. Participants in the corticosteroid group received an intra-articular injection of 1 ml methylprednisolone (40 mg/ml) dissolved in 4 ml lidocaine (10 mg/ml); participants in the placebo group received an injection of 1 ml isotonic saline with 4 ml lidocaine (10 mg/ml).

The exercise intervention consisted of a facility-based, functional and individualized exercise program supervised by a trained physiotherapist (CB) three times weekly for 12 weeks. Details about the exercise program can be found elsewhere[22,25].

MRI

MRI of the target knee was performed on a 3 Tesla Siemens Verio® system using a dedicated 15 channel send/receive knee coil.