

Are ultrasonographic signs of inflammation predictors for response to intra-articular glucocorticoids in knee osteoarthritis?

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Abstract

Objective

To investigate the predictive value of ultrasound (US) characteristics for the effect of intra-articular glucocorticoids in knee osteoarthritis (OA).

Methods

In this prospective cohort study, 62 patients with symptomatic knee OA (clinical knee OA criteria, pain > 4 on a Numerical Rating Scale (NRS; 0-10)) received an intra-articular glucocorticoid injection (40 mg triamcinolone acetonide). Patients with NRS pain ≤ 4 at 4 weeks were defined as responders. On inclusion, demographics, clinical data (body mass index, local swelling) knee x-rays and knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire were collected. Six US features were assessed including: effusion, synovial hypertrophy, Baker's cyst, infrapatellar bursitis, meniscal protrusion and cartilage thickness. Stepwise multiple logistic regression analyses with forward selection were conducted to identify possible predictors

Results

At 4 weeks, 42% of the study participants reached a NRS ≤ 4; an effect comparable to existing literature. Regression analyses showed that patients who used analgesics at baseline were less likely to have a good response. The small proportion of patients with infrapatellar bursitis was more likely to respond to the injection.

Conclusion

No patient, disease or US characteristic of inflammation, turned out to be a reliable and clinically meaningful predictor for the effect of intra-articular glucocorticoids after four weeks in knee OA.

Key words

osteoarthritis, knee, musculoskeletal ultrasound, intra-articular injection

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Received on March 15, 2014; accepted in revised form on May 28, 2014.

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Introduction

Osteoarthritis (OA) is a common joint disorder, with the knee being one of the most frequently involved sites. So far, no disease-modifying drugs for OA are available. Therefore, current guidelines for the medical management of patients with knee OA suggest multimodal treatment combining pharmacological (*e.g.* analgesics, local glucocorticoids) and non-pharmacological (education, lifestyle management and exercise) measures (1-3). In these guidelines, administration of intra-articular glucocorticoids is not advised as standard treatment, but can be considered in patients with a flare of knee pain, especially in those with local signs of inflammation.

The effect on pain of intra-articular glucocorticoids in knee OA is well established. It is clear but relatively short-lived (max. 3-4 weeks), with numbers needed to treat of 3-4 (4). Although few side effects of intra-articular injections are reported, it is an invasive procedure which not all patients are willing to undergo. Furthermore, because of the prevalent nature of the condition, many intra-articular injections could be prevented if it were possible to make an *a priori* selection of patients with better chance of response.

So far, evidence for solid predictors for response to intra-articular glucocorticoids in knee OA is lacking as studies on this topic are sparse. Based on the anti-inflammatory properties of glucocorticoids, one might expect a higher chance of response in patients with signs of inflammation. This is supported by previous research which suggested that intra-articular glucocorticoids are more beneficial in patients with clinical joint effusion (5, 6). However, studies using ultrasonography (US) show inconsistent results concerning the predictive value of inflammation (effusion, synovial hypertrophy) for response to intra-articular glucocorticoids (7, 8). It has even been suggested that patients without inflammation are better responders (9).

In search of possible inflammatory and mechanical features which might predict response, it is attractive to use US as imaging modality. It is a very practical tool and has shown good construct

validity (10, 11) and moderate to good interobserver reliability (12, 13) in knee OA. Furthermore, it is able to visualise (peri)articular structures (inflammatory as well as non-inflammatory) which are involved in the process of knee OA (10, 14).

Therefore, in this study, we investigated the predictive value of US characteristics for the effect of intra-articular glucocorticoids in knee OA.

Patients and methods

Study design

This prospective study was conducted in the framework of a specialised knee and hip OA outpatient clinic. All patients also received multimodal treatment comprising education, physical therapy, step up analgesics (acetaminophen, non-steroidal anti-inflammatory drugs, tramadol) and advice on gradual weight reduction when indicated (15). The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095). All patients signed an informed consent.

Patients

From November 2010 to May 2011, 62 patients fulfilling the clinical American College of Rheumatology (ACR) criteria for knee OA criteria (16) were included. Radiographic OA was not an inclusion criterion. The symptomatic knee was appointed as index joint. If patients had bilateral knee OA, the most symptomatic knee was selected. All included patients were treated with blind intra-articular injection of 40 mg triamcinolone acetonide in addition to standardised multimodal treatment. No aspiration of synovial fluid was performed and no local anesthetic was injected. Following injection, patients were recommended to rest and avoid weight-bearing activities for 24h. Use of anticoagulants was not an exclusion criterion.

Exclusion criteria were: pain score on numerical rating scale (NRS, 0-10) of ≤ 4 , other rheumatic or orthopaedic diseases leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints or limitations of the knee OA, orthopaedic procedures planned within the next three months,

Competing interests: none declared.

or cognitive or sensorimotor problems interfering with filling out questionnaires.

Data acquisition

On inclusion, demographics, clinical data (body mass index, local swelling) and knee x-rays were collected. Posterior-anterior fixed flexion and lateral knee radiographs were graded using Kellgren and Lawrence (K&L) systematics (17). Follow-up was planned at 4 weeks by telephone. The NRS on pain was recorded on both visits. At baseline, patients were asked to fill out the Dutch version of the KOOS (Likert-scale version) questionnaire, (with permission, www.koos.nu). Pain and function subscales were calculated as normalised scores (0–100, where 100 signifies most severe complaints).

Ultrasonography

Ultrasonography was performed by two rheumatologists and a post-doc physician, who were trained in musculoskeletal US and previously involved in inter reader reliability research of the applied US protocol. A previously developed US protocol was used which showed moderate to good inter observer reliability (12). Because we introduced a new investigator and as interobserver agreement of synovial hypertrophy was previously dissatisfactory, we performed renewed calibration sessions. Renewed interobserver agreement tests in 23 patients showed moderate to good results for all items (Table I). We did not repeat interobserver reliability tests in infrapatellar bursitis, because of the very low prevalence of this item. The protocol is based on results of previous US studies (especially the OMERACT definitions) (18, 19) and pathophysiologic concepts of knee OA. It focuses on two domains, comprising inflammatory (synovial hypertrophy and effusion and bursitis), and mechanical aspects (medial meniscus protrusion, Baker's cyst and cartilage thickness). We did not include power Doppler measurements as this seems to be a rather rare feature in knee OA (14), and power Doppler is a very machine dependent tool, which hampers generalisability.

Table I. Interobserver agreement US features.

Observation	Kappa (n=23)
Effusion	1.00
Synovial hypertrophy	0.65
Baker's cyst	1.00
Meniscal protrusion	0.59
Correlation coefficient (95%CI)	
Medial femoral cartilage thickness	0.77 (0.60-0.95)
Lateral femoral cartilage thickness	0.74 (0.57-0.92)
Intercondylar notch cartilage thickness	0.75 (0.57-0.94)

Clinical evaluation and US examination were obtained on the same day. The investigator performing US was unaware of clinical and radiographic results. The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy) with a 35 mm linear transducer (frequency 8–15 MHz). The complete US investigation took about ten minutes per patient. The US protocol comprised the following items:

1. Effusion: a ≥ 4 mm hypoechoic or anechoic intra-articular material that is displaceable and compressible in the suprapatellar recess, evaluated using a longitudinal scan with the leg in passive full extension.
2. Synovial hypertrophy: an abnormal hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible of ≥ 2 mm in the suprapatellar recess, measured with the leg in full extension with a longitudinal scan.
3. Meniscal protrusion: protrusion of meniscal tissue out of the joint space > 3 mm from the joint line, evaluated at the medial joint space with the knee in full extension with a longitudinal scan
4. Infrapatellar bursitis: an enlarged infrapatellar bursa (> 2 mm) on both longitudinal and transverse scans with the knee in 45° flexion.
5. Baker's cyst: a hypo-anechoic area between the semimembranosus and medial gastrocnemius tendon examined with the patient in prone position on the dorsal/medial side of the fully extended knee applying a transverse and longitudinal scan. The maximum diameter was measured (mm) in a transverse plane.
6. Cartilage thickness: an anechoic band with sharp hyperechoic margins,

measured perpendicular to the surface at the intercondylar notch and at the medial and lateral condyle, with the transducer immediately above the patella in a transverse plane and with the knee in maximum flexion. A summary score of cartilage thickness was computed.

Statistical analysis

Descriptives were computed. Frequencies, means and Standard Deviations (SD) were calculated where appropriate. Effect of intra-articular injection: NRS pain ≤ 4 at four weeks after injection was the primary outcome measure. Decrease in NRS pain at T=4 weeks was a secondary outcome measure. Patients with NRS pain ≤ 4 at 4 weeks were defined as responders. Outcomes were checked for confounding/effect modification on the following items: age, BMI, KOOS at baseline, gender, K&L score and use of analgesics.

Prediction of response

To compare responders and non-responders on baseline characteristics, chi-square tests and *t*-tests were performed, where appropriate. To determine potential predictors of response to intra-articular glucocorticoids (NRS pain ≤ 4 at 4 weeks), stepwise multiple logistic regression analyses with forward selection ($p < 0.20$) were conducted. The following variables were included in the model: age, gender, body mass index (BMI), knee swelling at physical examination at baseline, use of analgesics at baseline, NRS pain and KOOS ADL at baseline and US features (*i.e.* Baker's cyst, effusion, synovial hypertrophy, infrapatellar bursitis, meniscal protrusion

and cartilage thickness). As effusion synovial hypertrophy and infrapatellar bursitis are considered to be expressions of the same pathophysiologic inflammatory process and we were especially interested in inflammation, we performed *post hoc* analyses with composite inflammatory determinant score (yes/no). It was considered to be positive if effusion and/or synovial hypertrophy and/or infrapatellar bursitis (Composite inflammatory score A) or effusion and/or synovial hypertrophy (Composite inflammatory score B) were present. Predictor variables with an association of $p < 0.20$ to the dependent variable were retained in the final model. Anticipating a response rate of 40%, we would need 70 patients to include 3 predictors (rule of thumb: 1 predictor for 10 responders) in our final regression model. Statistical analysis was performed using the statistical software package Stata10 (Stata-Corp, Texas, USA).

Results

Baseline characteristics

From November 2010 to April 2011, a total of 62 knee OA patients fulfilling our inclusion and exclusion criteria received an intra-articular injection with glucocorticoid. Baseline characteristics are shown in Tables II and III. Table II shows a typical (20, 21) knee OA cohort with predominantly overweight women with moderate type OA according to radiographic K&L score.

Table II. Baseline characteristics.

Number of patients (n)	62
Age (years) (SD)	55.4 (8.7)
Women (%)	58
BMI (kg/m ²) (SD)	30.2 (5.6)
Pain at baseline ^o (NRS) (SD)	6.6 (1.0)
Kellgren & Lawrence score (%)	
0	11
1	26
2	35
3	21
4	7
KOOS adl (score)* (SD)	55.7 (18.0)
Use of analgesics (%)	53

*Knee Osteoarthritis Outcome Score; function in daily living: normalised data (0–100) in which 0 indicates no complaints;

^oNRS: Numerated Rating Scale (0–10) in which 0 indicates no complaints and 10 indicates maximal complaints and 100 indicates maximal complaints.

Table III. Baseline prevalence of US features.

Effusion (n, %)	15 (24%)
Synovial hypertrophy (n, %)	14 (23%)
Meniscal protrusion (n, %)	41 (66%)
Infrapatellar bursitis (n, %)	6 (10%)
Baker's cyst (n, %)	20 (32%)
Cartilage thickness (mean) (mm, SD)	1.9 ± 0.4
Composite inflammatory score A*	46 (44%)
Composite inflammatory score B*	35 (42%)

*Composite inflammatory score A: effusion and/or synovial hypertrophy and/or infrapatellar bursitis

*Composite inflammatory score B: effusion and/or synovial hypertrophy

Table IV. Characteristics of patients injection group (responders vs non-responders).

	Responders (n=26)	Non-responders (n=36)
Age (years) (SD)	55 (7.8)	56 (9.4)
Women (%)	46	67
BMI (kg/m ²) (SD)	29.2 (5.0)	31.0 (6.1)
Pain at baseline (NRS 0 - 10)(SD)	6.3 (1.2)	6.8 (1.0)
Pain at 4 weeks (NRS 0 - 10)(SD)	3.0 (1.0)	6.2 (1.0)
Analgesics users (%) [†]	46	78
KOOS adl (mean, SD)	51 (20)	59 (16)
Ultrasonography features		
Baker's cyst (%)	35	31
Effusion (%)	19	28
Synovial hypertrophy (%)	23	22
Infrapatellar bursitis (%)	15	6
Meniscal protrusion (mm) (SD)	69	64
Cartilage thickness (mm)(SD)	2.0 (0.4)	1.8 (0.4)

[†]Statistical significant (p -value < 0.05).

Response to intra-articular injection

At four weeks, 42% of the injection group reached a NRS ≤ 4 . Mean values of NRS pain decreased from 6.6 (± 1.0) at baseline to 4.9 (± 1.9) at T=4 weeks. No confounding/effect modification was established.

Prediction of response to intra-articular glucocorticoids

Baseline characteristics for responders versus non-responders are shown in Table IV. Except for pain and condylar cartilage thickness, no significant baseline differences between the subgroups were found. Table V shows the results of the final logistic regression model with clinical and US variables ($p < 0.20$) predicting response of intra-articular glucocorticoids at four weeks.

Discussion

In this pragmatic clinical trial we found that, besides perhaps infrapatellar bursitis, no other patient, disease or US characteristic of inflammation turned out to be a reliable and clinically mean-

ingful predictor for the effect of intra-articular glucocorticoids in knee OA.

Our study confirms the somewhat controversial earlier finding that inflammation is no predictor for response to intra-articular triamcinolone acetate in knee OA. As glucocorticoids have strong anti-inflammatory properties, one would expect a better effect of intra-articular injection in patients with clinical or US signs of inflammation. So far, results from previous studies on this subject are conflicting. Some studies suggested a beneficial effect of intra-articular glucocorticoid injection in patients with signs of inflammation (5, 6). Others do not find any difference in effect or even higher response rates in patients without inflammatory signs (7–9). In our study, none of the beforehand suspected inflammatory candidates for prediction of response (*e.g.* knee swelling and effusion and synovial hypertrophy detected with US) proved to be an actual predictor. Thus, so far, the rationale for reserving intra-articular injection for patients with signs of lo-

Table V. Results of the final logistic regression model predicting response of intra-articular corticosteroids at four weeks.

Predictor	OR (95 % CI)	p-value
Analgesic use at baseline	0.19 (0.05-0.70)	0.01
Infrapatellar bursitis	11.46 (1.21-108.20)	0.03
KOOS-adl	0.96 (0.92-1.00)	0.04
Gender (female)	0.41 (0.12-1.41)	0.16

cal inflammation, is not supported by evidence.

Surprisingly, we did demonstrate that, infrapatellar bursitis – although not very prevalent – seemed to be associated with higher response rates in our cohort. This is not easy to understand. Firstly, infrapatellar bursitis is a localised problem and not necessarily a sign of integral inflammation of the knee. Furthermore this bursa does not communicate with the joint. So the mechanism of effect of an intra-articular injection is not completely clear. Although diffusion of part of the intra-articular glucocorticoid or systemic effects could play a role. As the prevalence of this bursitis is very low with resulting wide confidence intervals, it might well be a spurious finding. In this cohort of 6 patient with infrapatellar bursitis two were non-responders and 4 were responders.

We recognise that there are several limitations to this study. First, we chose to administer blind instead of US guided injections. As US guided injections in the knee have higher accuracy of needle placement, higher response rate would have been possible. On the other hand, our response rates are comparable with other cohorts and blind injections are much more common in daily practice. We realise that this study comprises of a limited number of study participants. Based on our sample size calculation, we were allowed to include 3 instead of 4 predictors in the final model. However this rule does not take the effect size into account. Because we were interested in clinically meaningful predictors,

the current amount of patients would have enabled us to detect the ones with a major contribution to prediction.

In conclusion, despite the use of ultrasound, it was not possible to predict efficacy of intra-articular glucocorticoids based on the presence of inflammation.

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