The OA Trial Bank: Meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids

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Word count:
Abstract: 249
Manuscript: 3998

Abstract

Objective: To evaluate the efficacy of intra-articular (IA) glucocorticoids for knee or hip osteoarthritis in specific subgroups of patients with severe pain and inflammatory signs using individual patient data (IPD) from existing trials.

Design: Randomized trials evaluating one or more IA glucocorticoid preparation in patients with knee or hip osteoarthritis , published from 1995 up to June 2012 were selected from the literature. Individual patient data obtained from original trials included patient and disease characteristics and outcomes measured. The primary outcome was pain severity at short-term follow-up (up to 4 weeks). The subgroup factors assessed included severe pain (≥70 points, 0 to 100 scale) and signs of inflammation (dichotomized in present or not) at baseline. Multilevel regression analyses were applied to estimate the magnitude of the effects in the subgroups with the individuals nested within each study.

Results: Seven out of 43 published randomized clinical trials (n=620) were included. Patients with severe baseline pain had a significantly larger reduction in short-term pain, but not in mid-and long-term pain, compared to those with less severe pain at baseline (Mean Difference 13.91; 95% 1.50 to 26.31) when receiving IA glucocorticoid injection compared to placebo. No statistical significant interaction effects were found between inflammatory signs and IA glucocorticoid injections compared to placebo and to tidal irrigation at all follow-up points.

Conclusions: This IPD meta-analysis demonstrates that patients with severe knee pain at baseline derive more benefit from IA glucocorticoid injection at short term follow-up than those with less severe pain at baseline.

Keywords: IPD analysis; osteoarthritis; knee; hip; IA glucocorticoid; injection

Background

Given the small to moderate effect size of symptomatic treatments in osteoarthritis (OA) and the heterogeneity of OA patients, treatment guidelines for OA have addressed the need for research on clinical predictors of response to these different treatments.[1, 2] However, the identification of responsive subgroups is challenging. In order to ensure that the right patients receive the right treatment, it is essential to use appropriate methodologies. Some trials have focussed on the different OA joint groups (e.g. hand, hip, knee or foot) and for treatment specifically aimed at certain OA subgroups such as osteotomy for varus knee OA.[3] However, to design trials on every available treatment for every identified subgroup would be expensive and unrealistic.

Post hoc analyses within individual trials are frequently applied to identify subgroups with different treatment responsiveness. However, such analyses are not powered a priori and therefore are subject to a high risk of type I and type II errors .[4, 5] A methodologically robust method is to test for subgroup-treatment interaction effects.[3] This method carries a much smaller risk of false-positive results but requires large sample sizes to detect the interaction between subgroup variables and treatment. A meta-analysis for quantifying interaction effects using Individual Patient Data (IPD) may help to overcome the power problem in individual trials.[6] In a meta-analysis using IPD, in which the data of several trials are pooled, the interaction effects between subgroups and treatment can be reliably assessed and potential confounders at both study and individual patient levels can be adjusted for.[6]

The OA Trial Bank initiative was therefore commenced in 2010 to collect and analyse IPD of published RCTS in OA.[7] The OA trial bank brings together data from individuals with OA recruited for published RCTs from different countries around the world to form a databank.

Intra-articular (IA) glucocorticoid injections are frequently applied in knee or hip OA patients who are unresponsive to non-invasive treatments or oral non-steroidal anti-inflammatory drugs (NSAIDS). An IA glucocorticosteriod injection is particularly recommended for OA patients with signs of local inflammation.[2, 8-11] The Cochrane systematic review on the effectiveness of IA glucocorticoid injection in knee OA found some evidence for the efficacy of IA glucocorticoid injections compared to IA placebo for pain and patient global assessment at one week post injection, with evidence also for continuing efficacy at two and three weeks post-injection.[10] It is however suggested that especially patients with clinical evidence of inflammation would benefit more from IA glucocorticoid injections.[12] However, Jones et al. could not confirm these findings.[13] To date, no IPD analyses have been performed to study interaction effects in frequently applied OA interventions. The primary aim of this

study is to evaluate the efficacy of IA glucocorticoids for knee or hip OA in specific subgroups of patients according to the severity of pain and inflammatory signs, over both short and long term follow-up, using individual patient data from published trials.

Methods

We carried out an IPD meta-analysis of RCTs studying the efficacy of IA glucocorticoid injections in patients with hip or knee OA. Full study protocol details have been published.[7]

Study selection

The following inclusion criteria were applied for studies to be included in the OA trial bank for the current study purpose:

Type of studies

All RCTs, including crossover trials, evaluating one or more IA glucocorticoid preparations in patients with OA of the knee or hip. There were no language restrictions.

Participants

Participants have a diagnosis of OA of the knee or hip:

(1) according to the American College of Rheumatology (ACR) classification criteria.[14, 15]

(2) on the basis of detailed clinical and/or radiographic information.

Studies including a subgroup of knee or hip OA patients were also included.

Types of interventions

All IA glucocorticoid preparations used for treatment of OA of the knee or hip in humans, compared to control treatments including: placebo,, IA hyaluronan/hylan, other doses of IA glucocorticoids, usual conservative treatments, or compared to different types of injection procedures of glucocorticoids. Trials were grouped into three different comparisons: 1. IA glucocorticoid injection versus placebo; 2. IA glucocorticoid injection versus hyaluronic acids and 3. IA glucocorticoid injection versus tidal irrigation.

Types of baseline assessments

(1) Important confounders: as a minimum baseline severity of pain, age and gender should have been assessed at baseline.

(2) *If available:*

Signs of inflammation should have been assessed at baseline, either by physical examination (warmth, effusion) or by additional testing (ultrasound, MRI, biopsy, serum CRP/ESR).

Types of outcomes

The minimum criterion for inclusion was reporting of pain. The primary outcome measure was pain severity at short-term (up to 4 weeks) follow-up. Secondary outcomes included pain severity at mid-term (closest to 3 months) and long-term follow-up (closest to 12 months). Information regarding other OMERACT III core set of outcome measures including physical function and patient global assessment were analysed when feasible.[16]

Subgroup analyses

Subgroup analyses were performed for the primary and secondary outcomes in the subgroups of patients with and without severe pain (≥70 on 0-100 scale) and with and without inflammatory signs (yes/no).

Identification of eligible studies

The following databases were searched from 1995 (based on availability of data sets and authors) until 19 June 2012 for RCTs of IA glucocorticoid versus control treatment for OA of the knee or hip: the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); EMBASE, Web of Science, Scopus, Cinahl, Pedro and the controlled trial registers. (Appendix 1) In addition, reference lists were hand searched for further identification of published work. Potential on-going studies were searched by Horizon scanning documents from Arthritis Research UK (including European Patent Office; Intellectual Property Office; NHS - Database of Uncertainties about the Effects of Treatments (DUETS); ISRCTN Registry of Clinical Trials; ClinicalTrials.gov; UKCRN Portfolio Database; Australian New Zealand Clinical Trials Registry; Netherlands Trials Register; German Clinical Trials Register).

Two review authors (MM, SB) independently selected citations based on titles and abstracts. Full articles were obtained for the citations that met the eligibility criteria and assessed by the two review authors independently. The OA Trial Bank board members were consulted if consensus was not reached.

Data collection and transfer

All corresponding authors of eligible trials were approached and asked for their data following the OA Trial Bank protocol and terms.[7] All data-deliverers signed the data delivery license agreement. Data sets were accepted in any kind of format, provided that variables and categories were adequately labelled within the data set or with a separate codebook. The original data collection files were kept in

their original version and saved on a secured server at the Erasmus MC University Medical Center in Rotterdam. To ensure quality, all data were checked for consistency and numbers were compared with published papers. In case of differences, authors were contacted and discrepancies were resolved.

Risk of Bias assessment

The methodological quality of the studies was assessed using the twelve criteria recommended by the Cochrane Collaboration and were evaluated independently by two researchers (Appendix 2). The criteria were scored as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear'. Any disagreements between the review authors were resolved by discussion, including input from the OA Trial Bank board members. A study with a low risk of bias was defined as fulfilling six or more of the criteria items.

Data extraction

From the published papers, details on the interventions and comparator groups were obtained. Data obtained from the original databases included patient characteristics (age, gender, BMI), disease specific characteristics (ACR criteria, radiographic information, signs of inflammation, duration of complaint), study characteristics (types of interventions, doses) and outcome measures measurements (pain, function and global perceived recovery). All randomized patients with a database record were entered in the pooled database and all individual trials were assigned an individual random trial number.

Data analyses

The primary outcome was pain severity at short-term follow-up. If available we used the VAS pain measure, otherwise the WOMAC pain score was used, followed by other Likert scores but converted into a VAS 0-100 scale. Secondary outcomes included pain severity assessed at other follow-up durations (mid-term and long-term follow-up), physical functioning (standardized to 0 to 100 scale) and global assessment.[16]

The heterogeneity of trials was measured using I-square – the inconsistency among studies that cannot be explained by chance.[17] An additional analysis was performed as appropriate by excluding the trials causing heterogeneity in order to reach an I-square index of below 50.

Overall effects between the different comparative treatments on the primary outcome pain at all follow-up points were estimated using multilevel regression analyses. The analyses were adjusted for baseline pain, age and gender. Data were not imputed since all trials included had less than 15% of missing values.

The subgroup factors were, based on consensus, standardised to a.) severe pain, yes (≥70 points) or no (<70 points) and b.) signs of inflammation (yes or no). In addition separate pooled analysis was undertaken for the different definitions of inflammation.
All analyses were repeated for hip and knee OA participants separately where more than one RCTs could be included in the analyses.

Multilevel regression analyses were applied to estimate the magnitude of the effects in the different subgroups with the individuals nested within each study, adjusted for age and gender. To assess potential subgroup effects, a random-effects linear regression model was used to calculate interaction effects. The model included the dependent variable, i.e. pain intensity at follow-up (0-100 scale) and independent variables, i.e. treatment (glucocorticoid injection or control), the effect modifier (severe pain (yes or no) or signs of inflammation (yes or no)), and an interaction term (pain BY treatment or inflammation BY treatment). The interaction effects represent the combined effects of severe pain or inflammation on pain severity and therefore represent the difference in effectiveness for the subgroup effects of IA glucocorticoid injection on pain severity. Interaction effects were only tested for these comparisons including more than one RCT. Interaction effect with p-value less than 0.05 was considered as statistically significant, indicating that the outcome depends on the severity of pain or signs of inflammation at baseline. For statistical significant interaction terms, separate subgroup effects were calculated to assist the interpretation of the results. The clinical significance of the interaction effect was estimated by the effect size (Cohen's d - the adjusted effect estimate of the interaction term divided by the pooled standard deviation of the baseline pain scores). An effect size of 0.2 was considered small and 0.5 moderate, while and effect size >0.8 indicates a large clinical effect.[18]

Results

Description of the studies

Of the 420 publications identified from the literature search, 43 publications met the eligibility criteria. Of these, 13 were duplicate publications and therefore 30 publications were eligible. A total of 23 authors were for several reasons unresponsive (Figure 1).[12, 13, 19-39] Following written request, authors of seven studies agreed to participate and were able to deliver their data to the OA Trial Bank. These seven published RCTs included 620 patients fulfilling the eligibility criteria and were included in the OA Trial Bank for the current study purpose.[40-46] Of these, four studies [41, 43, 45, 46] compared glucocorticoids (n=116) with placebo (n=107), two studies [41, 44] compared glucocorticoids (n=72) with

hyaluronic acid (n=71), two studies [40, 46] compared glucocorticoids (n=104) and tidal irrigation (n=92) and one study [42] compared glucocorticoids with botulinum toxin injections (n=60). An overview of the included studies is presented in Table 1. Five studies [40, 42-44, 46] included patients with knee OA only and two [41, 45] included hip OA patients only. All studies reported on pain at both short and mid-term follow-up, while six studies reported on function outcomes (WOMAC) and three studies reported on a global assessment.

Table 2 presents the baseline characteristics of the study participants for each comparison. The average age was about 65 years and 49.7% were women. Severe pain was present in 34.4% of the total population, with the highest number in the studies comparing glucocorticosteriod injections with hyaluronic acids. Inflammatory signs, measured in five studies, were present in 41.8% of all subjects.

The risk of bias scores of the individual studies are presented in Table 3. All studies scored positive on at least 5 out of 11 points, with all studies scoring positive on the items 'method of randomization', 'compliance acceptable' and 'timing of outcome assessment'. Two studies scored negative on all three blinding issues.[40, 41]

Overall treatment effects

A significant overall effect on the primary outcome pain severity at short-term follow-up was seen of IA glucocorticoid injection compared to placebo (Mean Difference (MD) 18.72 (95% Confidence Interval (CI) 13.04 to24.41)) and compared to hyaluronic acid (MD 9.38 (95%CI 5.69 to13.09) (Table 4).

At long-term follow-up there was a significant overall negative effect of IA glucocorticosteriod injection compared to tidal irrigation (MD -4.57 (95%CI -7.40 to-1.74)).

At mid-term a significant overall positive effect of glucocorticoid injection was found compared to placebo (MD 10.00 (95%CI 3.88 to 16.13) but no statistical significant differences were found at long-term following when glucocorticoid injection was compared to placebo.

Subgroup analyses among knee and hip OA patients separately revealed overall significant effects of IA glucocorticoid injection compared to placebo at short-term in both patient populations; 13.93 (95%CI 6.41 to 21.46) and 24.54 (95%CI 16.28 to 32.82), respectively. At mid-term, a significant overall effect was seen of IA glucocorticoid injection compared to placebo in hip OA patients only (13.58 (95%CI 3.53 to 23.62) but not in knee OA patients (6.90 (95%CI -0.66 to 14.47)). No significant treatment effects were found at long-term follow-up in either the knee or hip OA subgroups (data not shown).

Baseline pain severity and treatment effect

A significant positive interaction (13.91; 95%CI 1.50 to 26.31) was found between severe pain at baseline and the treatment effect of IA glucocorticoid injection compared to placebo at short-term follow-up (Table 5). This was illustrated by the statistically significantly larger reduction in short term pain (adjusted effect estimate 28.54; 95%CI 13.56 to 43.51) in patients with severe pain compared to those with less severe pain at baseline (14.97; 95%CI 9.57 to 20.37) when receiving IA glucocorticoid injection compared to placebo. No significant interaction effects were found between severe pain and the treatment effect of IA glucocorticoid injection compared to placebo at mid- and long-term follow-up. No significant interaction effects were found between severe pain and the treatment effect of IA glucocorticoid injection compared to hyaluronic acid and tidal irrigation.

Subgroup analysis on knee OA patients also revealed a significant interaction (18.04; 95%CI 1.87 to 34.20) between severe pain and IA glucocorticoid injection compared to placebo at short-term follow-up. This was illustrated by the statistically significantly larger reduction in short term pain (adjusted effect estimate 27.28; 95%CI 6.72 to 47.83) in patients with severe pain compared to those with less severe pain at baseline (9.54; 95%CI 2.65 to 16.44) when receiving IA glucocorticoid injection compared to placebo. No significant interaction was found at mid-term follow-up (5.15; 95%CI -11.79 to 22.10). No significant interaction effects between severe pain and IA glucocorticoid injection compared to placebo were found in hip OA patients at any follow-up point (data not shown).

Baseline inflammatory signs and treatment effect

No significant interaction effects were found between inflammatory signs and IA glucocorticoid injections compared to placebo and compared to tidal irrigation at all follow-up points (Table 6).

The interaction effect between inflammatory signs detected by ultrasound and IA glucocorticoid injection compared to placebo at short-term follow-up was not statistically significant (9.04; 95%CI -0.71 to 18.80) (Table 7).

No significant interaction effects were found between inflammatory signs and IA glucocorticoid injection and placebo in knee OA patients on both short-term (-3.83; 95%CI -18.98 to 11.31) and mid-term (1.49; 95%CI -13.96 to 16.94) follow-up. No analyses could be performed on hip OA patients only, since only one study was available.

Discussion

The individual patient data meta-analyses on IA glucocorticoid injection showed that there is an overall positive, and clinically relevant (>10 points on 0-100 scale), effect of IA glucocorticoid injection compared to placebo at short- and mid-term follow-up, with estimate reduction in pain of 18.7 and 10.0 (on a 0-100 scale) respectively. Compared to hyaluronic acid injection, an overall positive effect of IA glucocorticoid injection was found at short-term only. Patients with severe baseline pain had a significantly larger reduction in short term pain (adjusted effect estimate 28.54; 95%CI 13.56 to 43.51) than those with less severe pain at baseline (14.97; 95%CI 9.57 to 20.37) when receiving IA glucocorticoid injection compared to placebo. The difference was well presented with the interaction term between the treatment and the subgroup indicator in the multilevel regression model (Table 5). Similar result was observed in knee OA with a slightly greater difference between severe versus less severe knee pain at baseline (18.04; 95%CI 1.87 to 34.20). However, no firm conclusions could be drawn on the subgroup effect of inflammation, though a positive non-significant trend was noted for the effectiveness of IA glucocorticoid injection in the subgroup of patients with inflammatory signs measured by ultrasound. No statistically significant interaction effects were found in the subgroup of hip OA patients.

IA glucocorticosteriod injections are commonly applied to relieve symptoms of knee and hip OA; however, factors predicting the response to treatment are poorly understood. Maricar et al. (2013) aimed to determine factors associated with response to IA glucocorticosteriod injection by summarizing the literature.[47] The authors of this review concluded that no consistent predictors of response were identified for IA glucocorticosteriod injection in knee OA. However, effusion, absence of synovitis, delivering injections under US guidance, structural severity of disease and pain were features that were reported by individual studies as enhancing the response of IA glucocorticosteriod injections.[12, 13, 40, 43, 48]

The current meta-analysis aimed to identify the possible subgroup effects of severe pain and inflammatory signs. In agreement with Maricar et al. (2013) we found a significant and clinically relevant interaction effect (moderate effect with effect size 0.56) between severe pain at baseline and IA glucocorticosteriod injection. Severe pain was defined as a pain score higher than 70 points on a 0-100 scale. Earlier studies have indicated that radiographic severity of knee OA would be predictive to response on IA glucocorticosteriod injection [40, 49] while self-perceived symptom severity was not

found predictive for the treatment response in two other studies.[12, 50] The fact that different outcomes are seen between these studies and our meta-analyses could be due to the small sample size of the individual studies and the difference in studies included. Following our protocol, we analyzed the subgroup effect of patients with severe pain on an easy applicable measure for clinical practice. The results of this meta-analysis indicate that both patients with and without severe pain at baseline clinically benefit from IA glucocorticosteriod injection compared to placebo at short-term follow-up. Although patients with severe pain achieved significantly more benefit from IA glucocorticosteriod injection compared with patients with less severe pain, with a clinically relevant difference of 14 points on a 0 to 100 pain scale. This effect seems to be most predominant in knee OA patients since no significant interaction effects were found in the small hip OA patient subgroup. However, no statistical significant subgroup effects were found on any of the other follow-up points or between the other comparisons. This is however consistent to the overall effect of IA glucocorticosteriod injection, primarily showing significant effects at short-term follow-up, with the largest, and clinically relevant, effect found at short-term follow-up, comparing IA glucocorticosteriod injection to placebo.

OA is sometimes considered a non-inflammatory degenerative disease, however it is now recognized that inflammation may play a role in the pathogenesis in at least some patients. IA glucocorticosteriod injections have been used for the treatment of OA for many years and it has been suggested that these injections are most effective in patients with evidence of inflammation on physical examination. The main indication for IA glucocorticoid use is to provide pain relief in patients whose condition remains unresponsive to or intolerant of oral systemic medication.[45] However, conflicting effects have been found in the different subgroups and most individual studies were underpowered to examine subgroup effects in OA populations.[12, 43] In our pooled IPD meta-analysis a non-significant positive interaction was found for the short- and mid-term treatment response on IA glucocorticosteriod injection compared to placebo for patients with inflammatory signs, detected by ultrasound. However, by removing baseline pain from the adjusted analyses, the positive interaction between the ultrasound inflammation and the treatment was no longer seen. Therefore it seems that severe pain is the best and most easy measure to predict the treatment response of IA glucocorticosteriod injections of patients with knee or hip OA.

Strengths and limitations

The key strength of this study is that we used individual patient data from seven trials giving the study greater power than any of the individual studies that have been conducted on potential predictors of response for the treatment of IA glucocorticoid injection in patients with knee or hip OA. There was

some heterogeneity within the first comparison (see Table 4). Therefore we repeated the analyses for both short-and mid-term subgroup effects of IA glucocorticoid injections compared to placebo by excluding the study of Chao et al. (reduction of I^2 to 0%). This did however result in comparable effect estimates. In addition, all analyses performed were predefined and described in our published protocol.[7] There are also several limitations. Based on the literature we approached the authors of 43 potential eligible publications, including 13 duplicate publications. Of the 30 potentially available studies only seven authors agreed to participate. As a consequence, only two studies could be included for the analyses comparing IA glucocorticoid injection with hyaluronic acid and tidal irrigation and a possible selection bias might have occurred. This proves the challenge of collecting data of performed RCTs. Authors of nine publications indicated that the data were no longer available and data rights of an additional three RCTs were sold. This strengthens the rationale for the recent initiative of journals to require authors to make trial data accessible on reasonable request.

We included the study of Boon et al. which was not included in the subgroup analyses since this was the only study comparing IA glucocorticoids with botulinium toxin. Since our intention was to include all studies with non-surgical comparators, we decided to include this study in the OA Trial Bank despite that this intervention was not pre-specified in our protocol paper.

We planned to perform subgroup analyses on both severe pain and signs of inflammation, however only four of the six studies included in the analyses actually measured signs of inflammation. As a consequence, the subgroup effect of inflammation could not be calculated for the comparison between IA glucocorticoid injection and hyaluronic acids and long-term analysis was only possible for the comparison between IA glucocorticoid injection and tidal irrigation. In addition, the subgroup analyses for inflammation are likely to be underpowered due to the low number of subjects included. Since inflammation was measured and reported in many different ways, it is therefore recommended that special interest groups will reach consensus on these measures to allow meta-analyses in future.

Finally, we were forced to make some amendments on our published protocol.[7] We intended to adjust for at least age, gender and BMI. However, since not all studies collected data to calculate the BMI, we were not able to adjust the analyses for BMI.

Clinical implications

This individual patient data meta-analysis shows that patients with severe pain at baseline significantly more benefit from IA glucocorticoid injection than those with less severe pain at short term follow-up. However, both patients with and without severe pain show clinical relevant effects (>10 points on 0-100

pain scale) of IA glucocorticoids at short-term follow-up. No firm conclusions can be drawn on the additional benefit of IA glucocorticoid in the subgroup of patients with inflammatory signs due to the limited power of the study for this subgroup. Since severe pain is easy to measure in patients in daily practice, we suggest to use this measure to identify those patients with knee or hip OA who would benefit the most from IA glucocorticoid injections.

Acknowledgements

KD is part funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Research and Care West Midlands and by a Knowledge Mobilisation Research Fellowship from the NIHR.

Author contributions

MvM, KD, MD, WZ, JWB, TM, SLSL, and SMAB-Z were involved in the study design and contributed to the interpretation of the results. MvM contacted the potential data deliverers, coordinated the data collection, and performed the data analyses. NA, IA, FB, JC, RL and PR provided the data and were responsible for the data-collection and individual study-designs. MvM wrote the manuscript together with KD, MD, WZ, JWB, TM, SLSL, SMAB-Z, NA, IA, FB, JC, RL and PR . MvM and SMAB-Z have full access to the study data. All authors approved the final manuscript.

Role of funding source

Dutch Arthritis Foundation

Conflict of interest

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Flow diagram of search and included studies