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Primary care

Corticosteroid injections for osteoarthritis of the knee: meta-analysis

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Abstract

Objectives To determine the efficacy of intra-articular corticosteroid injections for osteoarthritis of the knee and to identify numbers needed to treat.

Data sources Cochrane controlled trials register, Medline (1966 to 2003), Embase (1980 to 2003), hand searches, and contact with authors.

Inclusion criteria Randomised controlled trial in which the efficacy of intra-articular corticosteroid injections for osteoarthritis of the knee could be ascertained.

Results In high quality studies, the pooled relative risk for improvement in symptoms of osteoarthritis of the knee at 16-24 weeks after intra-articular corticosteroid injections was 2.09 (95% confidence interval 1.2 to 3.7) and the number needed to treat was 4.4. The pooled relative risk for improvement up to two weeks after injections was 1.66 (1.37 to 2.0). The numbers needed to treat to get one improvement in the statistically significant studies was 1.3 to 3.5 patients.

Conclusion Evidence supports short term (up to two weeks) improvement in symptoms of osteoarthritis of the knee after intra-articular corticosteroid injection. Significant improvement was also shown in the only methodologically sound studies addressing longer term response (16-24 weeks). A dose equivalent to 50 mg of prednisone may be needed to show benefit at 16-24 weeks.

Introduction

Knee pain is relatively common. Around a quarter of people aged 55 years or more in the United Kingdom and the Netherlands have persistent pain, and one in six will consult their general practitioner.[1] Osteoarthritis is the single most common cause of disability in older adults, with 10% of patients aged 55 or more having painful disabling osteoarthritis of the knee, a quarter of whom are severely disabled.[1] With no cure (excluding joint replacement), treatment is directed at pain relief and improvement or maintenance of function.

Intra-articular injection of steroid is a common treatment for osteoarthritis of the knee. Clinical evidence suggests that benefit is short lived, usually one to four weeks.[2] The short term effect of steroids shown by controlled trials and clinical experience vary, however, with some patients seen by rheumatologists achieving a significant and sustained response beyond a few weeks. This may be explained by only one injection usually being given in clinical trials and at a lower dose (20 mg) than the 40 mg triamcinolone recommended by the American College of Rheumatologists.[3] Pain scores may also be an insensitive outcome measure.

Concern has been expressed that long term treatment could promote joint destruction and tissue atrophy.[2] Studies of cartilage damage, however, tend to suggest that changes are more likely due to the underlying disease than the steroid injection.[4]

Three papers have reviewed the general management of osteoarthritis of the knee, one specifically on corticosteroid injections, but no meta-analysis has been undertaken.[1 4–6] We therefore performed a meta-analysis to determine whether intra-articular injections of corticosteroid are more efficacious than placebo in improving the symptoms of osteoarthritis of the knee.

Methods

We searched the Cochrane controlled trials register, Medline (1966 to 2003), and Embase (1980 to 2003) using the MeSH terms triamcinolone; prednisolone; prednisone; hydrocortisone; adrenal cortex hormones; osteoarthritis; knee; injections, intra-articular; and randomized controlled trial, and the non-MeSH terms injections; randomised controlled trial; and corticosteroid and steroid. Authors of included studies were contacted for details of any further work. The reference lists were scrutinised for relevant papers.

Our selection criterion was randomised placebo controlled trials in which the efficacy of intra-articular corticosteroids for osteoarthritis of the knee, of any duration, could be assessed. We considered improvement as the most important patient oriented outcome. Terms used to determine the discrete outcomes were distinct improvement, subjective improvement, decreased pain, overall improvement, clinically relevant outcomes, and response to the osteoarthritis research scale.[7–12] Numbers needed to treat were calculated from dichotomous outcomes.[13]

The two authors independently assessed the methodological quality using the Jadad scoring system.[14] Consensus was reached through discussion. Data extraction was similarly achieved. Data were analysed with Review Manager 4.1 (Update Software, Oxford). We calculated the relative risk and number needed to treat for improvement. An a priori subgroup analysis was conducted for study quality, dose of drug, duration of effect, specialty of injector, and condition of the knee. The dose equivalents were obtained from elsewhere.[15] The conduct of this review was undertaken according to the QUOROM statement.[16]

Results

Ten trials met the inclusion criteria (fig 1).[2 7–12 17–19] An additional paper examined intra-articular corticosteroid injections postoperatively, but we did not consider this paper in the review.[20] Table 1 shows the quality scores of the included studies, and table 2 summarises details of the studies and improvements attained.

Six studies provided data on improvement of symptoms of osteoarthritis of the knee after intra-articular corticosteroid injections (fig 2). These showed a significant improvement (rela-

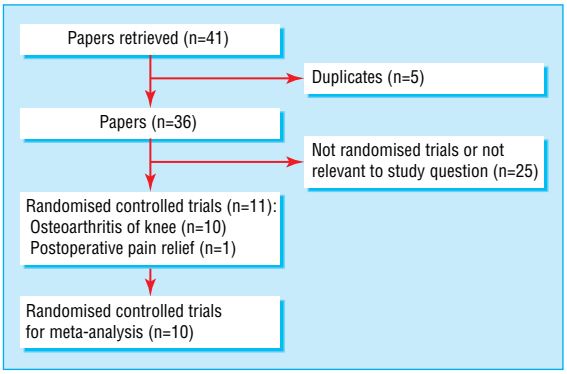

Fig 1 Summary of search results

tive risk 1.66, 95% confidence interval 1.37 to 2.01). For the statistically significant studies the number needed to treat to obtain one improvement was between 1.3 and 3.5. No important harms were reported other than transient redness and discomfort. Only one study investigated potential loss of joint space and found no difference between corticosteroid and placebo up to two years.[2]

Neither of the two high quality studies were statistically significant for improvement at 16 to 24 weeks, but the pooled result gave a relative risk of 2.09 (1.20 to 3.65) with a number needed to treat of 4.4 based on this result (fig 3). Significant heterogeneity was found when the one low quality study was included. The result was non-significant by random effects analysis. Figure 4 shows the results of pooling the 100 mm visual analogue scale for five studies. When standard deviations were not reported, we assigned a value of 30, as this was the highest reported value and was taken as a conservative estimate. This result is statistically significant. We found no results for pain 16 weeks after injection. A funnel plot of the six studies suggested that there was an absence of small studies with small effects (fig 5). The smallest study had 12 patients and the largest 71.

A similar result was found for improvement up to two weeks for the high dose studies. The effect at 16 to 24 weeks for these studies was the same as the two high quality studies. It was not possible to make a definitive analysis of the clinical conditions of the knee. The patients seemed to have mainly mild to moderate osteoarthritis. The dose equivalent to prednisone varied from 6.25 mg to 80 mg.

Discussion

Intra-articular injections of corticosteroid improve symptoms of osteoarthritis of the knee. Effects were beneficial up to two weeks and at 16 to 24 weeks. This is the first meta-analysis on this topic and the first review to show benefits of such injections in improvement of symptoms, which may extend beyond 16 weeks. We also report clinically significant numbers needed to treat, ranging between 1.3 and 3.5 patients. The one study that investigated potential loss of joint space found no difference between corticosteroid and placebo up to two years.[2] This study also used a higher dose of triamcinolone (40 mg) than most of the other studies (20 mg) and gave repeated injections (every three months for two years).

Responses to intra-articular corticosteroids injections vary between the clinical experience of rheumatologists, where some patients have a significant and sustained response, to the short term benefit shown by randomised controlled trials.[4] Trials tend to use one injection only and at lower doses than the recommended 20 mg triamcinolone.[3] Subjective pain scales may also be an insensitive outcome measure in this condition.[4]

One limitation of our review is possible publication bias, in that by missing unpublished trials or those that showed negative effects we may have overestimated the benefits of corticosteroid injections. We believe, however, that our comprehensive, systematic search strategy enabled us to identify most research in this discipline. Another limitation of our study was the small size of the included studies.

Unlike other reviews we report improvement in symptoms, as we believe this is a more important patient oriented outcome than increases in range of movement or pain reduction.[21] Only the review by Pendleton and coworkers attempted to pool the results of papers, but they did not perform a meta-analysis, rather they reported the number of studies that showed benefits compared with those that did not and a median effect size.[5] Apart from the fact that other reviewers did not pool their data, we had the benefit of access to an article that was in press.[12] When this was added to the other two studies, the pooled result was statistically significant for the two high quality studies.[12] Larger studies are needed to confirm these findings.

The dose of corticosteroid required to improve symptoms is not clear from our review. The equivalent dose of prednisone varied from 6.25 mg to 80 mg.[12 19] A dose of 20 mg triamcinolone (equivalent to 25 mg of prednisone) seems to be efficacious for pain control at two weeks. Only one study used 40 mg triamcinolone, and this found a benefit at 24 months for night pain and stiffness on one scale but not on another.[2] This study also gave repeated injections and monitored loss of joint space (reporting no difference). The three studies that reported improvement at 16 weeks used different cortisones. The two

Table 1 Jadad quality scores for 10 studies of intra-articular corticosteroid injections for osteoarthritis of the knee

Study	1	2	3	4	5	6	7	8	9	10	11	Jadad score[14]
Cederlöf 1966[7]	+	+	?	?	+	?	+	+	+	+	–	3
Dieppe 1980[8]	+	+	?	+	?	–	+	+	+	+	+	3
Friedman 1980[9]	+	+	?	+	+	+	+	+	+	+	–	5
Gaffney 1995[10]	+	+	?	+	–	–	+	+	–	+	+	3
Jones 1996[17]	+	+	?	+	+	–	+	–	–	+	+	3
Miller 1958[18]	+	+	?	+	–	?	+	+	–	+	–	2
Ravaud 1999[11]	+	+	?	+	+	+	+	+	+	+	+	5
Raynauld 2003[2]	+	+	?	+	–	–	+	+	+	+	+	3
Smith 2003[12]	+	+	?	–	+	+	+	+	+	+	+	5
Wright 1960[19]	+	+	?	+	+	+	?	+	–	+	–	5

Numbers 1-11 follow Pedro format (www.cchs.usyd.edu.au/pedro/); Jadad score is calculated from different set of criteria[14]: 1=eligibility criteria specified; 2=patients randomised to groups; 3=concealment of allocation; 4=groups similar at baseline; 5=patients blinded; 6=practitioners administering intervention blinded; 7=assessors blinded; 8=measurements of key outcomes obtained from >85% of patients; 9=intention to treat analysis; 10=statistical comparisons between groups; 11=point measures and measures of variability provided.
+Criterion clearly satisfied.
–Criterion not clearly satisfied.
?Unclear whether criterion was satisfied.

Table 2 Details of included studies with outcomes on improvement in osteoarthritis of knee

Study, location	Condition	Details of patients	Injectors; nature of injection	Outcome	Jadad score
Cederlöf 1966,[7] Sweden	History of aching after exertion, not trauma related and positive radiograph but no noticeable cartilage destruction	≥40 years; no details on sex or duration of osteoarthritis	Surgeons; aspiration and intra-articular steroid injection (Meticortelone 2 ml) compared with placebo (saline); prednisone equivalent 50 mg	No significant difference between groups at 1, 3, and 8 weeks. Results reported as distinct improvement. At one week, 18/26 in experimental group, 14/25 in control group; eight weeks, 17/26 in experimental group, 19/25 in control group had continued improvement compared with baseline	3/5
Dieppe 1980,[8] United Kingdom	Bilateral symptomatic osteoarthritis of knees	Mean 65 years; eight females, four males; most had grade 2-4 radiographic changes. Duration of osteoarthritis 7.5 years	Rheumatologist; aspiration and intra-articular steroid injection (triamcinolone hexacetonide 20 mg) compared with placebo (saline); prednisone equivalent 25 mg	Small, transient reduction in pain and tenderness compared with placebo. At one week, subjective improvement in 10/12 in experimental group, 1/12 in control group. Visual analogue scale at one week: mean 36 (SD 29) in experimental group, 70 (30) in control group	3/5
Friedman 1980,[9] United States	Mild to moderate changes on radiograph	42-75 years; mean duration of osteoarthritis 24 months for corticosteroid group and 36 months for placebo group	Rheumatologist; aspiration and intra-articular steroid injection (triamcinolone hexacetonide 20 mg) compared with placebo (saline); prednisone equivalent 25 mg	Steroid provided short term pain relief; at one week but not at 4, 6, 8 weeks. At one week described as decreased pain; 15/17 in experimental group, 12/17 in control group	5/5
Gaffney 1995,[10] United Kingdom	38% synovial fluid and knee pain for six months	Mean 67 years; 60 females, 24 males. Mean duration 6.7 years for corticosteroid group and 7.1 years for placebo group	Rheumatologist; aspiration and intra-articular steroid injection (triamcinolone hexacetonide 20 mg) compared with placebo (saline); prednisone equivalent 25 mg	Steroid provided short term pain relief. Benefit at one week but not at six weeks. At one week overall improvement; 33/42 in experimental group, 21/42 in control group. Visual analogue scale: mean 21.7 (SD 20.7) in experimental group, 43.1 (28.7) in control group	3/5
Jones 1996,[17] United Kingdom	Clinical and radiological osteoarthritis of knee	Mean 71 years; 23 males, 37 females. No details on duration of osteoarthritis	Rheumatologist; aspiration and intra-articular steroid injection (methylprednisolone 40 mg) compared with placebo (saline); prednisone equivalent 40 mg	Steroid provided short term pain relief. Responders at eight weeks: 28/30 in experimental group, 9/30 in control group	3/5
Miller 1958,[18] Scotland	Primary osteoarthritis	No details on age, sex, or duration of osteoarthritis	Unclear who injected; intra-articular steroid injection (hydrocortisone 50 mg) compared with lactic acid; local anaesthetic; saline; and mock injection. Injections given five times at two week intervals; prednisone equivalent 12.5 mg	Steroid did not provide improvement better than placebo at six weeks or six months follow up after completion of treatment. Term used was "improved." At six months: 4/34 in experimental group, 2/34 in control group; at 16 weeks 6/37 in experimental group, 8/36 in control group	2/5
Ravaud 1999,[11] France	Most had knee effusion; all had osteophytes and minimal joint space narrowing	Mean 63-67 years; 66 females, two males. No details on duration of osteoarthritis	Rheumatologist; intra-articular steroid injection (cortivazol 1.5 ml) with or without joint lavage compared with placebo (saline); prednisone equivalent 37.5 mg	Steroid provided short term pain relief up to four weeks but no effect at 24 weeks. At one week clinically relevant improvement in pain, 16/25 in experimental group and 7/28 in control group. At 24 weeks: 12/25 in experimental group and 6/28 in control group. Visual analogue scale at one week: (n=24) mean 23.7 (SD 26.2) in experimental group, (n=21) 45.7 (26.6) in control group	5/5
Raynauld 2003,[2] Canada	Kellgren and Lawrence grade 2 or 3	63 years; 67.5% female. Mean duration of osteoarthritis 9.8 years for corticosteroid group and 8.7 years for placebo group	Rheumatologist; intra-articular steroid injection (triamcinolone 40 mg) and placebo (saline) every three months for two years; prednisone equivalent 50 mg	Area under curve showed benefit for night pain and stiffness: 34 in each of experimental and control groups. At one year patient visual analogue scale: 34.32 (SD 20.9) in experimental group, 31.1 (21.1) in control group	3/5
Smith 2003,[12] Australia	Radiograph grade 2 or 3	Mean 66-67 years; 44 males, 27 females	Orthopaedic surgeon and rheumatologist; intra-articular steroid injection (methylprednisolone acetate 120 mg) after joint lavage compared with placebo; prednisone equivalent 80 mg	Steroid better than placebo only at four week follow up but not at 8, 12, or 24 weeks. Osteoarthritis Research Society response occurred: at two weeks 25/38 in experimental group, 15/33 in control group; at 24 weeks 16/38 in experimental group, 7/33 in control group. Visual analogue scale at two weeks: mean 20.8 (SD 30) in experimental group, 24.7 (30) in control group	5/5
Wright 1960,[19] United Kingdom	Denominator knees not pooled	No details on personal characteristics or duration of osteoarthritis	Internal medicine specialist; intra-articular steroid injections (hydrocortisone acetate 25 mg and hydrocortisone tertiary-butylacetate 25 mg) compared with placebo (injection vehicle). Four injections given at two weekly intervals; prednisone equivalent 6.25 mg	Both steroids provided transient pain relief at two weeks (25 patients, 38 knees)	5/5

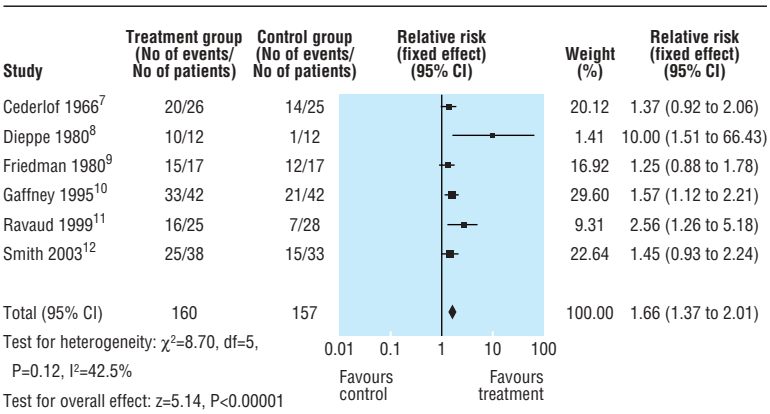

Fig 2 Improvements up to two weeks after steroid injection in knee

studies using high doses showed a statistically significant difference suggesting that higher dose steroids may give a longer benefit.[2 12] It is not clear to whom the results of this study would apply.[11 12] All the studies were done in hospital settings.

One study found that predicting benefit was not possible.[17] In contrast to another study, those who had synovial fluid aspirated had a better response.[10] This only occurred in the intervention group, ruling out that aspiration was associated with accurate placement of the needle. Another explanation is that the presence of knee effusion is correlated with the presence of synovitis and that intra-articular steroids my be effective against the inflammation.[4] One study recommended joint lavage combined with steroid injection if a knee effusion persisted after one or two steroid injections eight to 10 days apart.[4] Joint lavage was either efficacious (at two weeks) or nearly efficacious (efficacious when controlled for severity from radiographic evidence at 24 weeks) for more than 16 weeks.[11 12]

Evidence supports short term (up to two weeks) improvement of symptoms from intra-articular corticosteroid injection for osteoarthritis of the knee, and the only methodologically-sound studies addressing longer term response (16-24 weeks) also show significant improvement. Doses of 50 mg equivalent of prednisone may be needed to obtain benefits at 16 to 24 weeks. Corticosteroid injection in addition to lavage needs further investigation. Currently no evidence supports the promotion of disease progression by steroid injections. Repeat injections seem to be safe over two years but needs confirmation from other studies.

Contributors: BA and FG-S were involved in extracting the data, appraising the article, and writing the paper. BA did the mathematical pooling; he will act as guarantor for the paper. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests: None declared.

Ethical approval: Not required.

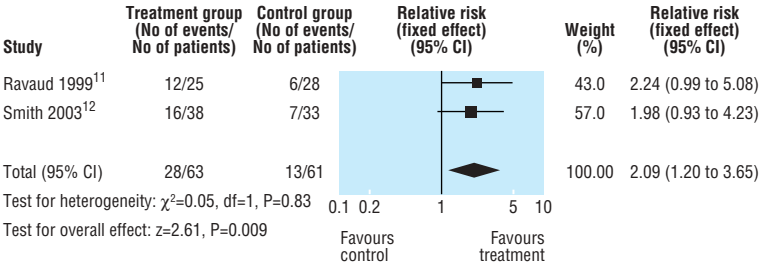

Fig 3 Improvements at 16-24 weeks after high dose steroid injection in knee for two high quality studies

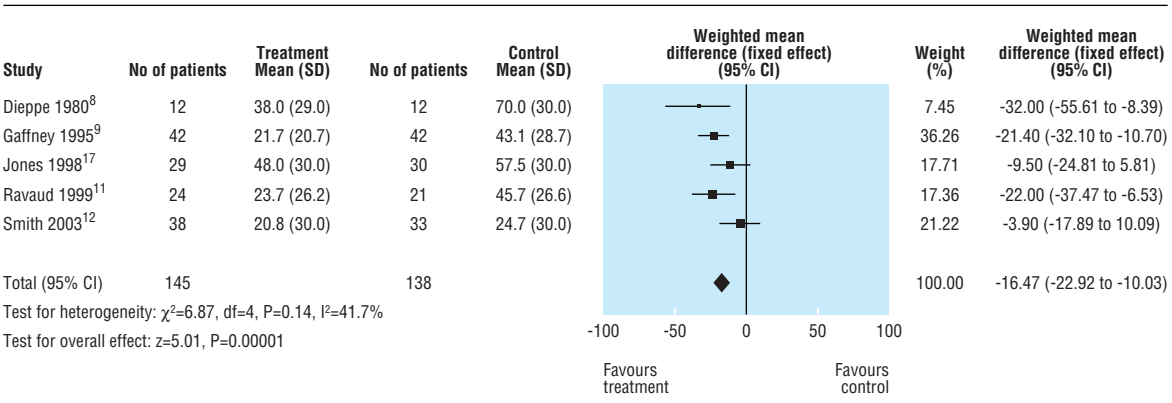

Fig 4 Visual analogue scale for pain up to two weeks after steroid injection in knee

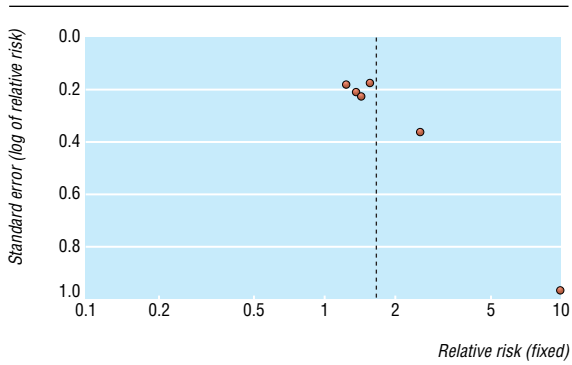

Fig 5 Funnel plot for corticosteroids compared with placebo

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What is already known on this topic

Intra-articular corticosteroids provide short term (two weeks) relief of symptoms of osteoarthritis of the knee

Concerns are that multiple injections may damage articular cartilage

What this study adds

Intra-articular corticosteroids are probably effective in improving symptoms of osteoarthritis of the knee for 16 to 24 weeks

The number needed to treat is 4.4

Higher doses of cortisone (equivalent to 50 mg prednisone) may be more effective than lower doses, especially after 16 or more weeks

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