Intraarticular corticosteroid for treatment of osteoarthritis of the knee (Review)

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2005, Issue 2

http://www.thecochranelibrary.com

WILEY
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Plain Language Summary</td>
<td>2</td>
</tr>
<tr>
<td>Background</td>
<td>2</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Results</td>
<td>3</td>
</tr>
<tr>
<td>Discussion</td>
<td>13</td>
</tr>
<tr>
<td>Authors' Conclusions</td>
<td>15</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>16</td>
</tr>
<tr>
<td>References</td>
<td>16</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>21</td>
</tr>
<tr>
<td>Index Terms</td>
<td>21</td>
</tr>
</tbody>
</table>

*Intraarticular corticosteroid for treatment of osteoarthritis of the knee (Review)*

Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Intraarticular corticosteroid for treatment of osteoarthritis of the knee

N Bellamy, J Campbell, V Robinson, T Gee, R Bourne, G Wells

Contact address: Nicholas Bellamy, Professor and Director, Medicine, Centre of National Research on Disability and Rehabilitation Medicine (CONROD), C Floor, Clinical Sciences Bldg., Royal Brisbane Hospital, Herston Road, Brisbane, Queensland 4029, AUSTRALIA. nbellamy@medicine.uq.edu.au.

Editorial group: Cochrane Musculoskeletal Group.
Publication status and date: Unchanged, published in Issue 1, 2006.


Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background
Osteoarthritis (OA) is a common joint disorder. In the knee, injections of corticosteroids into the joint (intra-articular (IA)) may relieve inflammation, and reduce pain and disability.

Objectives
To evaluate the efficacy and safety of IA corticosteroids in treatment of OA of the knee.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2003), MEDLINE, EMBASE, PREMEDLINE (all to July 2003), and Current Contents (Sept 2000). Specialised journals, trial reference lists and review articles were hand searched.

Selection criteria
Randomised controlled trials of IA corticosteroids for patients with OA of the knee: single/double blind, placebo-based/comparative studies, reporting at least one core OMERACT III outcome measure.

Data collection and analysis
Methodological quality of trials was assessed, and data were extracted in duplicate. Fixed effect and random effects models, giving weighted mean differences (WMD), were used for continuous variables. Dichotomous outcomes were analysed by relative risk (RR).

Main results
Twenty-six trials (1721 participants) comparing IA corticosteroid against placebo, against IA hyaluronan/hylan (HA products), against joint lavage, and against other IA corticosteroids, were included.

IA corticosteroid was more effective than IA placebo for pain reduction (WMD -17.79; 95% confidence interval (CI) -25.02 to -10.55) and patient global assessment (the RR was 1.44 (95% CI 1.13 to 1.82)) at one week post injection with an NNT of 3 to 4 for both, based on n=185 for pain on 100 mm visual analogue scale (VAS) and n=158 for patient global assessment. Data on function were sparse at one week post injection and neither statistically significant nor clinically important differences were detected.

There was evidence of pain reduction between two weeks (the RR was 1.81 (95% CI 1.09 to 3.00)) to three weeks (the RR was 3.11 (95% CI 1.61 to 6.01), but a lack of evidence for efficacy in functional improvement.
At four to 24 weeks post injection, there was lack of evidence of effect on pain and function (small studies showed benefits which did not reach statistical or clinical importance, i.e. less than 20% risk difference). For patient global, there were three studies which consistently showed lack of effect longer than one week post injection. However, all were fairly small sample sizes (less than 50 patients per group). This was supported by another study which did not find statistically significant differences, at any time point, on a continuous measure of patient global assessment (100 mm VAS).

In comparisons of corticosteroids and HA products, no statistically significant differences were in general detected at one to four weeks post injection. Between five and 13 weeks post injection, HA products were more effective than corticosteroids for one or more of the following variables: WOMAC OA Index, Lequesne Index, pain, range of motion (flexion), and number of responders. One study showed a difference in function between 14 to 26 weeks, but no differences in efficacy were detected at 45 to 52 weeks. In general, the onset of effect was similar with IA corticosteroids, but was less durable than with HA products.

Comparisons of IA corticosteroids showed triamcinolone hexacetone was superior to betamethasone for number of patients reporting pain reduction up to four weeks post injection (the RR was 2.00 (95% CI 1.10 to 3.63). Comparisons between IA corticosteroid and joint lavage showed no differences in any of the efficacy or safety outcome measures.

Authors’ conclusions

The short-term benefit of IA corticosteroids in treatment of knee OA is well established, and few side effects have been reported. Longer term benefits have not been confirmed based on the RevMan analysis. The response to HA products appears more durable. In this review, some discrepancies were observed between the RevMan 4.1 analysis and the original publication. These are likely the result of using secondary rather than primary data and the statistical methods available in RevMan 4.1. Future trials should have standardised outcome measures and assessment times, run longer, investigate different patient subgroups, and clinical predictors of response (those associated with inflammation and structural damage).

Plain Language Summary

Osteoarthritis (OA) is the most common form of chronic arthritis worldwide. Intraarticular (IA) corticosteroid products provide opportunity to treat OA in individual knee joints. To evaluate the efficacy, effectiveness and safety of IA corticosteroid products in knee OA, we have conducted a systematic review using Cochrane methodology. The analyses support the contention that the IA corticosteroid class of products is superior to placebo. The response is generally rapid, but may not be sustained in the longer term. Hyaluronic acid (HA) products, while slower in onset of action, may have a more sustained duration of benefit. The types of patients who may potentially benefit from IA corticosteroid versus HA therapy may differ. In general, sample size restrictions preclude any definitive comment on the safety of the IA corticosteroid class of products; however, within the constraints of the trial designs employed, no major safety issues were detected. Overall, the aforementioned analyses support the use of the IA corticosteroid class of products in the treatment of OA knee.

Background

Osteoarthritis (OA) is the most frequent cause of rheumatic complaints. OA of the knee is a leading cause of chronic disability in the United States (Felson 2000; Felson 2000a). OA is a group of distinct overlapping diseases, which may have different etiologies (causes), but have similar biologic, morphologic (form), and clinical outcomes. The disease processes involve the entire joint, including the articular cartilage (cartilage covering the bone surfaces in the joint), subchondral bone, ligaments, capsule, synovial membrane (membrane covering the bone ends), and periarticular muscles (muscles around the joint). Ultimately, the articular cartilage degenerates with fibrillation (the initial degenerative changes in OA, marked by softening of the articular cartilage and development of vertical clefts between groups of cartilage cells), exhibiting fissures, ulceration, and a thinning of the joint surface (Brandt 1996).

Intra-articular (IA) corticosteroid therapy was first used by Hollander in 1951 in Philadelphia to treat rheumatoid arthritis (Hollander 1953). The first clinical trial in OA was performed.
in 1958 by Drs Miller, White and Norton in Glasgow (Miller 1958). Twenty years after the first use of IA corticosteroids, the value of these injections was still questioned, with some authors of the opinion that the injections could reduce pain in the short term but were not helpful in treatment of the underlying arthritic lesion (Helfet 1974). Even fifty years after the introduction of IA corticosteroid therapy, concern was expressed regarding the masking of pain which allowed the patient to resume activity but possibly cause further destruction to the joint (Brandt 2001). In the last few years, the efficacy of IA corticosteroids has been reviewed in several publications (Ayral 2001; Creamer 1997; Gossec 2004; Haraoui 2002; Kirwan 1997; Kirwan 2001; Towheed 1997).

In 1995, the American College of Rheumatology (ACR) published guidelines for the treatment of OA of the knee (Hochberg 1995). These were updated in 2000 (ACR 2000) and state that, for mild symptomatic OA, treatment may include non-pharmacologic methods (patient education, physical and occupational therapy and other therapies), and pharmacologic therapy (including non-opioid oral and topical (i.e. applied to skin) analgesics). For patients who are unresponsive to this regimen, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is considered appropriate. IA corticosteroid injection is recommended for patients with knee OA, particularly when signs of local inflammation with joint effusion (build-up of fluid within the joint) are present. Patients with severe symptoms of OA of the knee may require surgical intervention, e.g. osteotomy (operation intended to promote healing of the joint) or total joint arthroplasty (replacement of the joint with artificial components).

Although our review is restricted to OA of the knee joint, IA corticosteroids have also been evaluated at other joints, including: elbow, shoulder, wrist, hip, heel (McColl 2000), metacarpophalangeal and metatarsophalangeal joints, and lumbar facets (Rozental 2000).

IA corticosteroids may provide short term pain relief. Long term benefit has yet to be established. A systematic review of IA steroid injections for knee OA with meta-analysis concluded that the beneficial effect started one week after injection and could last for three to four weeks (Godwin 2004). Evidence from another meta-analysis supported short term (up to two weeks’) benefit in general, with some longer term benefit lasting for 16 to 24 weeks (Arroll 2004). In a journal supplement devoted to the role of the general practitioner in managing OA and chronic musculoskeletal disease, these injections were recommended in combination with other non-pharmacological and pharmacological therapies (McColl 2001). McColl reported decreased pain and increased function for up to six weeks with injections into joints that showed evidence of joint effusion (McColl 2000). A European League Against Rheumatism (EULAR) task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials recommended IA injection of long-acting steroid for acute exacerbation (sudden worsening) of knee pain, especially if accompanied by effusion (Pendleton 2000). A clinical review of the medical management of OA by Walker-Bone (Walker-Bone 2000) concluded that “there was good evidence to support the judicious use of IA corticosteroids in patients with knee OA, but because of the potential for multiple IA injections to accelerate cartilage damage”, they should not be monotherapy for patients with chronic, stable OA. Two orthopaedic reviews (Noerdlinger 2001; Rozental 2000) have been completed. Noerdlinger recommended the judicious use of injectable corticosteroids for inflamed tissue followed by appropriate rehabilitation; this regimen provided pain relief and sped-up the healing process. They stressed the importance of proper technique. Rozental concluded that corticosteroid injections provided significant pain relief, especially in combination with non-steroidal anti-inflammatory drugs (NSAIDs), rest and physical therapy. In an evidence-based review of the management of OA in the primary care setting, Lane (Lane 1997) concluded that IA corticosteroids could relieve pain and inflammation but that the effect was of very short duration and so such therapy should only be used infrequently. The potential effect of corticosteroids on disease progression is still hypothetical and is the subject of clinical evaluation (Pelletier 2002). It is evident that controversy still exists in the literature as to whether IA corticosteroids are beneficial in the long term or whether the response is measured only in days.

**OBJECTIVES**

To conduct a systematic review of randomised controlled trials (RCTs) of IA corticosteroids for treatment of OA of the knee to evaluate efficacy and safety over both short and long term.

**RESULTS**

Bias 2001 reported a four-week, parallel-group, non-blind RCT performed at a single centre in Germany comparing one injection of four mg dexamethasone palmitate (Lipotalon) (equivalent to 2.5 mg dexamethasone) to one injection of 12 mg dexamethasone palmitate (equivalent to 7.5 mg dexamethasone) in 24 patients with activated inflammatory OA of the knee. The objective of this trial was primarily to investigate the pharmacokinetics of this formulation of the corticosteroid. Consequently, efficacy was not evaluated with a formal statistical analysis; rather a descriptive analysis was reported. The lowest disease activity index score (based on investigator rating of pain, temperature, effusion, and swelling) was recorded 16 days post injection in both groups. The largest reduction in pain was detected after an average of four days. No adverse events were recorded for any of the patients for the duration of the trial.

Caborn et al. (Caborn 2004) reported a 26-week, parallel-group, single-blind RCT performed at 14 centres in the United States...
comparing three weekly injections of Hylan G-F 20 to one IA injection of triamcinolone hexacetonide (Aristospan) in 218 patients with OA of the knee. The onset of action was faster in the triamcinolone hexacetonide group. However, treatment with Hylan G-F 20 resulted in a longer duration of effect. Both treatments were well tolerated with 10% of patients in each group reporting an adverse event that resulted in withdrawal from the trial.

The Caborn et al. trial (Caborn 2004) was single-blind and details regarding the method of randomisation were not published. The triamcinolone hexacetonide group received only one injection compared to the three injections administered to the Hylan G-F 20 group. Analgesic and NSAID usage were monitored throughout this trial. Patients with effusion of greater than 10 ml were excluded. Almost 30% of each treatment group had severe radiological ratings while approximately 60% in each group had moderate ratings.

Cederlof and Jonson (Cederlof 1966) reported an eight-week, parallel-group, double-blind RCT comparing IA prednisolone acetate (50 mg) to saline in 44 patients with OA of the knee. No differences were found between the two groups in the efficacy outcomes. No information on adverse events was reported in the publication.

Dieppe et al. (Dieppe 1980a, Dieppe 1980b) reported two trials in one publication. The first (Dieppe 1980a) was a six-week, parallel-group, single-blind RCT comparing IA triamcinolone hexacetonide (20 mg) to saline in 12 patients with bilateral OA of the knee. Maximum benefit in pain score was reported in the IA corticosteroid group one week post injection. No information on adverse events was reported. The second (Dieppe 1980b) was a one-week, cross-over, single-blind RCT comparing IA triamcinolone hexacetonide (20 mg) to saline in 16 patients with OA of the knee. The IA corticosteroid group was significantly (P value <0.05) better than saline for reducing pain and tenderness. No information on adverse events was reported.

Friedman and Moore (Friedman 1980) reported an eight-week, parallel-group, double-blind RCT comparing IA triamcinolone hexacetonide (20 mg) with placebo (suspending vehicle) in 34 patients with OA of the knee. Significantly less pain was reported by the IA corticosteroid group at one week post injection. Post injection flares (either increased pain, heat or swelling in the first 24 h after injection) occurred with similar frequency in both groups.

Frizziero and Pasquali Ronchetti (Frizziero 2002) reported a six-month, parallel group, single-blind RCT performed at a single centre in Italy comparing five weekly injections of Hyalgan to three weekly injections of methylprednisolone acetate in 99 patients with primary or secondary OA of the knee. The authors found an initial statistically significant difference in favour of methylprednisolone acetate at day 35 but not at day 180. The clinical effect with Hyalgan appeared more gradually but lasted longer than that of methylprednisolone acetate. Arthroscopic evaluations showed that Hyalgan was superior to methylprednisolone acetate in reducing the extent and grade of cartilage damage. No adverse events were reported in the Hyalgan group compared to two patients in the methylprednisolone acetate group, one resulting in withdrawal from the trial.

This RCT was one of the trials which examined the structural effects of Hyalgan using both arthroscopic and microarthroscopic examinations.

Gaffney et al. (Gaffney 1995) reported a six-week, parallel-group, double-blind RCT comparing IA triamcinolone hexacetonide (20 mg) with saline in 84 patients with OA of the knee. One of the purposes of this trial was to examine factors that could influence the clinical response. Pain relief was significantly greater (P value <0.01) in the IA corticosteroid group at one week post injection. This greater improvement in pain was associated with clinical evidence of an effusion (P value <0.05) and aspiration of synovial fluid at time of injection (P value <0.01). Two patients in the saline group withdrew at week one due to treatment inefficacy.

Jones et al. (Jones 1995) reported a 29-week, parallel-group, double-blind RCT comparing IA hyaluronic acid to IA triamcinolone hexacetonide (20 mg) in 63 patients with bilateral knee OA with effusion. Active treatment was always given to the worse knee. The contralateral knee received placebo injections of saline. This review compared IA triamcinolone hexacetonide in active knees to saline in the placebo knees in the 31 patients randomised to IA triamcinolone hexacetonide. No difference was found between the two groups in pain on a self-selected activity, which was the primary outcome measure. Seventy-four percent of the patients in the IA triamcinolone hexacetonide group withdrew during the trial, leaving 8 patients available for assessment at Week 29; 13/23 (57%) patients withdrew because of worsening of knee symptoms and slow improvement.

Jones and Doherty (Jones 1996) reported an eight-week, cross-over, double-blind RCT comparing IA methyl prednisolone acetate (40 mg) with saline in 60 patients with OA of the knee. Pain was significantly (P value <0.0001) reduced at three weeks post injection in favour of IA corticosteroid compared to saline. Similarly to the Gaffney trial (1995), the authors tried to identify clinical predictors of response. No clinical predictors of response were identified. Twelve patients withdrew prematurely from the trial: three due to worsening symptoms (two after IA corticosteroid and one after saline), one patient’s symptoms resolved, and eight withdrew for unrelated reasons.

Leardini et al. (Leardini 1987) reported a one-year, single-blind, parallel group RCT performed at a single centre in Italy comparing three weekly injections of Hyalgan to three weekly injections of methylprednisolone acetate (MPA) in 36 patients with OA of the knee. No statistically significant differences were found between the two groups in the clinical assessments. Local reactions were reported in three patients in the MPA group compared to four patients in the Hyalgan group.
This trial reported results on 40 joints of 36 patients (4 with bilateral disease).

Leardini et al. (Leardini 1991) reported a 60-day, open-label, parallel-group RCT performed at a single centre in Italy comparing three weekly injections of Hylan G-F 20 to one injection of betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan), which could be repeated during the study, in 100 patients with OA of the knee. No differences in pain or function were found between the two groups at the six months follow-up. Neither treatment worked well in females. One patient in the Hylan G-F 20 group withdrew because of an acute local reaction. One-fifth of the study population withdrew because of a lack of treatment efficacy. Only safety data have been extracted from this trial. Since the outcome variables had results that were not normally distributed, nonparametric statistical methods were used to analyze the data (e.g. change in median outcomes scores).

The Leopold et al. (Leopold 2003) trial was an independent trial not funded by the manufacturer of the hyaluronate-based product under study. The injection procedure was standardised by: 1) patient was in the supine position, 2) the injection was made superolaterally into the suprapatellar notch, and 3) patients were encouraged to refrain from strenuous activity for a day. However, effusions were aspirated in the HA group whereas they were not in the corticosteroid group. In addition, patients in the corticosteroid group were permitted to have one more injection any time during the study. The authors chose not to use the Aihlback radiographic grading system, ‘because three of the four stages include knees with a completely obliterated joint space’. This was the only trial to find a gender difference in treatment response.

Miller et al. (Miller 1958) reported a 24 week, parallel-group, double-blind RCT in 202 patients with OA of the knee. Five IA forms of injection were compared: lactic acid plus novocaine solution, novocaine solution, hydrocortisone acetate, and mock injection. This review compared hydrocortisone with saline. Twenty-one patients withdrew from the trial prematurely; five patients experienced relief after one injection, two patients had an acute reaction after injection, three patients were dissatisfied with treatment, two patients emigrated, and nine cases were lost to follow up. At six weeks post injection, there was no difference between any of the five groups based on percentage of patients improved. At the second assessment, six months after the first review, a further 14 patients were lost to follow up: six died of intercurrent disease and eight did not wish to continue. In the remaining 167 patients, there was no significant difference between the injections.

Pietrogrande et al. (Pietrogrande 1991) reported a 60-day, open-label, parallel-group RCT performed at three centres in Italy comparing five weekly injections of Hylan G-F 20 to three weekly injections of 6-methylprednisolone acetate (6-MPA) in 90 patients with OA of the knee. Although both treatments reduced the disease symptoms, 6-MPA had a more rapid action but did not last as long as Hylan G-F 20. At the final assessment, significant differences were found between the treatments for most outcome measures. One patient in the Hylan G-F 20 group had a local reaction which resolved spontaneously but was withdrawn due to lack of efficacy. No systemic adverse reactions were reported in either group.

Popov et al. (Popov 1989) reported a 20 day, parallel-group, double-blind RCT in 48 patients with OA of the knee and associated signs of limited synovitis in one knee. Five IA forms of injection were compared: triamcinolone acetonide (40 mg), hydrocortisone acetate (50 mg), aprotinin (50,000 units), polyvinylpyrrolidone and physiologic solution. Results indicated that triamcinolone acetonide and hydrocortisone acetate were significantly better than physiologic solution. Aprotinin and polyvinylpyrrolidone were no more effective than physiologic solution. No difference in efficacy between triamcinolone acetonide and hydrocortisone acetate was detected. Only one patient developed pain, swelling and itch after the second and third injections of aprotinin.

Pyne et al. (Pyne 2004) reported an eight-week, parallel-group, double-blind RCT comparing triamcinolone hexacetonide (THA) (20 mg) with methylprednisolone acetate (MPA) (40 mg) in 57 patients with OA of the knee. Both steroids provided short-term effectiveness. THA was more effective than MPA at week three in pain reduction, but lost its effect by week eight. MPA had a slower onset of action with benefit lasting to eight weeks. There were no dropouts in this trial. There were no reports of skin or soft tissue necrosis along the needle track.

Ravaud et al. (Ravaud 1999) reported a 24-week, placebo-controlled, 2x2 factorial design RCT in 98 patients with OA of the knee. Four groups were compared: 1) IA placebo (saline), 2) IA corticosteroid (Cortivazol 3.75 mg), 3) joint lavage and IA placebo (saline), and 4) joint lavage and IA corticosteroid (Cortivazol). The Cortivazol group had significantly (P value 0.02) improved pain VAS scores at week 4. The joint lavage group had significantly (P value 0.02) improved pain VAS scores at week 24. The combination therapy of joint lavage and IA corticosteroid produced an additive effect. The authors suggested that this combination “might be of faster and stronger efficacy” than the monotherapy regimens. Twenty-three patients withdrew prematurely from the trial; 19 due to inefficacy and four lost to follow up. The frequency of local discomfort was significantly (P value 0.012) higher with
joint lavage compared to IA injection.

Raynauld et al. (Raynauld 2003) reported a two-year, placebo-controlled, double-blind RCT comparing triamcinolone acetonide 40 mg (Kenalog) with saline (one cc) in 68 patients with OA of the knee. The authors found no difference between the two groups in joint space width after one and two years of treatment. At the end of the first year, the corticosteroid group had a significantly greater change in range of motion and a slightly greater improvement in pain compared to the saline group. Knee pain and stiffness were significantly improved over the two years in the steroid group but not in the saline group. The trial supported the long-term safety of IA steroid injections.

Smith et al. (Smith 2003) reported a 24-week, placebo-controlled, double-blind RCT comparing arthroscopic lavage plus methylprednisolone acetate (120 mg) with arthroscopic lavage plus normal saline in 77 patients with OA of the knee. There were no significant differences between the two groups for pain, stiffness or WOMAC or Lequesne assessments at any assessment. There was a significant difference at four weeks in the OARSI response criteria in favour of the MPA group (58%) compared to the placebo group (33%). There were no side effects from the IA injections. Three patients required further sutures of arthroscopy portals because of leakage of synovial fluid.

Tascioglu and Oner (Tascioglu 2003) reported a six-month, parallel-group, open-label RCT performed at a single centre in Turkey comparing three weekly injections of Orthovisc to three weekly injections of 6-methylprednisolone acetate (6-MPA) in 69 female patients with OA of the knee. In this trial, paracetamol (to a maximum of three g daily) was permitted but with restriction 48 hours prior to an assessment. The percentage of patients with uni/bilateral disease was not reported. A significant improvement was reported in both groups at week four in pain and Lequesne Index outcome measures. At three months, a significant improvement in pain and Lequesne Index was reported in favour of Orthovisc compared to 6-MPA. By six months, there was no difference between the two groups. No serious systemic adverse events were reported that could be related to the treatment. Similar percentages of patients reported knee pain after injection (Orthovisc 21%, 6-MPA 18%). There was no significant between group difference with respect to adverse events.

Tekeoglu et al. (Tekeoglu 1998) reported a 15-week, parallel-group, open-label RCT performed in Turkey comparing three weekly injections of Orthovisc to three weekly injections of betamethasone in 40 female patients with OA of the knee. In the short-term (week three), betamethasone was more effective than Orthovisc. In the long-term (week 15), Orthovisc was more effective than betamethasone. No local or systemic reactions were reported.

The Tekeoglu et al. (Tekeoglu 1998) trial allowed patients to take paracetamol as well. Again, the percentage of patients with uni or bilateral disease was not reported. In this RCT, patients were advised to rest for one day after injection 'to avoid overcharging the injected joint'.

Thorpe (Thorpe 1985) reported a 20-week, parallel-group, double-blind RCT comparing triamcinolone acetonide (10 mg) with methylprednisolone acetate (40 mg) in 44 patients with OA of the knee. No significant differences between the two groups were reported. This study provided evidence that a smaller quantity of IA triamcinolone acetonide was just as effective as a larger dose of IA methylprednisolone acetate. Both IA corticosteroids were well tolerated with no local or systemic adverse events being reported in either group.

Valtonen (Valtonen 1981) reported a 24-week, parallel-group, single-blind RCT comparing triamcinolone hexacetonide (20 mg) with a combination of betamethasone acetate and betamethasone disodium phosphate (BM) (6 mg) in 42 patients with OA of the knee with inflammation. Although both groups had significant improvement in pain one week post injection, triamcinolone hexacetonide was significantly superior (P value <0.005) compared to BM. This study evaluated duration of effect ‘as the time that elapsed between one IA injection of triamcinolone hexacetonide or BM and the patient’s request of further therapy or reinjection’. The duration of effect was significantly longer with triamcinolone hexacetonide. No patients withdrew prematurely from the trial. However, local pain after injection was reported by four of 21 patients in the triamcinolone hexacetonide group and one of 21 patients in the BM group.

Wright et al. (Wright 1960) reported a 40-week, cross-over, double-blind, three-arm RCT of hydrocortisone acetate (25 mg), hydrocortisone tertiary-butylacetate (25 mg) and suspending vehicle in 25 patients with OA of the knee. No significant differences were found between the two IA corticosteroids. Although injection of both IA corticosteroids resulted in improvement in pain compared to placebo at two weeks post injection, this improvement was only significant (P value 0.02) in the hydrocortisone tertiary-butylacetate group. Increased pain and stiffness lasting three days was reported in two knees treated with IA corticosteroid.

Young et al. (Young 2001) reported a four-week, placebo-controlled, double-blind RCT performed in Australia comparing arthroscopy followed by methylprednisolone acetate (120 mg) with arthroscopy followed by IA normal saline in 40 patients with OA of the knee. The objective of this trial was to investigate the effects of IA corticosteroid on macrophage infiltration, the expression of the chemokines MCP-1 and MIP-1alpha, and the expression of MMPs 1 and 3 and their inhibitors, TIMPs 1 and 2, in OA synovial tissue. The authors found a statistically significant reduction in the WOMAC score within the MPA group but no decrease in the placebo group. No safety data were reported in the publication.

Corticosteroid versus placebo: pain
Eight of the thirteen trials comparing corticosteroid with placebo reported some measure of pain.

Friedman (Friedman 1980) detected no statistically significant difference in the number of patients reporting pain reduction at either one week post injection (88% triamcinolone hexacetonide versus 71% vehicle), the relative risk (RR) was 1.25 (95% confidence interval (CI) 0.88 to 1.78; P value 0.2); or eight weeks post injection (65% triamcinolone hexacetonide versus 65% vehicle), the RR was 1.00 (95% CI 0.61 to 1.64; P value 1).

Using a numerical pain rating scale 0 to 10 and the Mann-Whitney U test, the Friedman publication reported a statistically significant difference (P value < 0.008) in favour of the triamcinolone hexacetonide group at one week post injection (Friedman 1980). Since no measure of dispersion (i.e. standard deviation) was reported, this outcome was not included in the RevMan analysis.

In Wright’s trial (Wright 1960), no statistically significant difference was detected in the number of knees reported as improved with respect to pain between hydrocortisone acetate (50%) and vehicle (36%) at two weeks post injection, the RR was 1.38 (95% CI 0.79 to 2.39; P value 0.3). However, in the same trial there was a statistically significant difference in the number of improved knees in the hydrocortisone tertiary-butylacetate group (66%) compared to the vehicle group (36%); the RR was 1.81 (95% CI 1.09 to 3.00; P value 0.02). Therefore, the number needed to treat (NNT) with hydrocortisone tertiary-butylacetate versus vehicle to achieve an improvement in pain two weeks post injection was three.

Ravaud (Ravaud 1999) defined responders in terms of at least a 30% decrease in pain VAS from baseline. A statistically significant difference was detected in the number of responders (64% Cortivazol versus 25% saline) at one week post injection; the RR was 2.56 (95% CI 1.26 to 5.18; P value 0.009). This is equivalent to a 39% risk difference, and an NNT of 2.6. No statistically significant difference was detected in the number of responders at four weeks (56% Cortivazol versus 29% saline), the RR was 1.96 (95% CI 0.99 to 3.87; P value 0.05); twelve weeks (52% Cortivazol versus 29% saline), the RR was 1.82 (95% CI 0.91 to 3.65; P value 0.09); or twenty-four weeks post injection (48% Cortivazol versus 22% saline), the RR was 2.24 (95% CI 0.99 to 5.08; P value 0.05).

Jones (Jones 1996) defined responders in terms of a 15% reduction in pain. A statistically significant difference was detected in the number of responders (47% methylprednisolone versus 15% saline) at three weeks post injection; the RR was 3.11 (95% CI 1.61 to 6.01; P value 0.0007). This equates to a 32% risk difference. The NNT with methylprednisolone versus saline to achieve an improvement at three weeks post injection in the number of responders was three.

Pain, assessed on a 0 to 100 mm VAS, showed a significantly greater improvement with IA corticosteroid than placebo at one week post injection (WMD (FE) -17.79; 95% CI -25.02 to -10.55; P value < 0.00001) (Dieppe 1980a; Dieppe 1980b; Gaffney 1995; Ravaud 1999). At two weeks post injection (Dieppe 1980a) RR was 0 (95% CI -20.00 to 20.00; P value 1); four weeks post injection (Dieppe 1980a; Ravaud 1999) RR was -7.96 (95% CI -20.01 to 4.09; P value 0.2); and six weeks post injection (Dieppe 1980a; Gaffney 1995) RR was -5.58 (95% CI -15.58 to 4.43; P value 0.3); no statistically significant differences were detected. A statistically significant difference in favour of Cortivazol was detected at 12 weeks post injection in the Ravaud (Ravaud 1999) trial (WMD (FE) -14.20; 95% CI -27.44 to -0.96; P value 0.04). Cortivazol was 31% more effective than saline. No statistically significant difference was detected at 24 weeks post injection, RR was -7.30 (95% CI -22.61 to 8.01; P value 0.3) (Ravaud 1999).

There was a statistically significant difference in favour of triamcinolone acetonide compared to saline in the Raynauld trial (Raynauld 2003) for WOMAC pain (0 to 100 mm VAS) at one year post injection (WMD -13.80; 95% CI -23.56 to -4.04; P value 0.006). Triamcinolone acetonide was 13% more effective than saline. No difference was detected at two years post injection (WMD -5.20; 95% CI -15.03 to 4.63; P value 0.3). The RevMan analysis differed from the Raynauld publication analysis in which no difference was found between the treatment groups for WOMAC pain at one year. The publication used a 2-sample t-test at one-year resulting in a P value of 0.22.

There was no statistically significant difference in pain at night (0 to 100 mm VAS) at one year post injection (WMD -5.10; 95% CI -14.66 to 4.46; P value 0.3); or at two years post injection (WMD 1.20; 95% CI -9.29 to 11.69; P value 0.8) (Raynauld 2003). The RevMan analysis differed from the original analysis in the Raynauld publication for pain at night at two years. The original analysis, which was based on area under the curve of the normalized values for night pain, reported a statistically significant difference (P value 0.0047) in favour of triamcinolone acetonide. However, using analysis of variance for repeated measurements, no statistically significant difference was found at two years (P value 0.74).

Corticosteroid versus placebo: function

Three of the 13 trials comparing corticosteroid with placebo reported a measure of physical function that could be extracted.

No statistically significant differences were detected in the Lequesne Index (scored 0 to 24) at one week post injection (WMD -2.20; 95% CI -4.87 to 0.47; P value 0.11), at four weeks (WMD -2.30; 95% CI -4.67 to 0.07; P value 0.06), 12 weeks (WMD -1.00; 95% CI -3.32 to 1.32; P value 0.4), or 24 weeks (WMD -1.20; 95% CI -3.58 to 1.18; P value 0.3) in the Ravaud trial (Ravaud 1999). No statistically significant differences were detected in the modified Health Assessment Questionnaire (scored 0 to 9) at one week post injection (WMD -0.10; 95% CI -0.96 to 0.76; P value 0.8) or at six weeks (WMD 0.30; 95% CI -0.62 to 1.22; P value
No statistically significant differences were detected in walking distance (measured in metres) at one week post injection (WMD 2.40; 95% CI -4.36 to 9.16; P value 0.5), or at six weeks (WMD -0.80; 95% CI -7.20 to 5.60; P value 0.8) (Gaffney 1995).

In the Raynauld trial (Raynauld 2003), there was a statistically significant difference between triamcinolone acetonide and saline at two years post injection for range of motion (ROM) measured in degrees (WMD 10.40; 95% CI 8.45 to 12.35; P value 0.00001), but not at one year (WMD -1.30; 95% CI -3.01 to 0.41; P value 0.14). Triamcinolone acetonide was 10% more effective than saline in improving range of motion at two years. The RevMan analysis differed from the original Raynauld analysis in which no difference had been found between the groups for range of motion at two years (P value 0.16, by analysis of variance for repeated measurements). Results showed no statistically significant differences for WOMAC Physical Function (0 to 100 mm VAS) at one year post injection (WMD -6.00; 95% CI -16.01 to 4.01; P value 0.2), or at two years (WMD -4.20; 95% CI -20.30 to 11.90; P value 0.6); or for 50-foot walking time at one year post injection (WMD -0.20; 95% CI -1.67 to 1.27; P value 0.8), or at two years (WMD -0.70; 95% CI -2.17 to 0.77; P value 0.4).

Corticosteroid versus placebo: global assessment

Nine out of 13 trials comparing corticosteroid with placebo reported a measure of patient global assessment.

The Ravaud and Raynauld trials (Ravaud 1999; Raynauld 2003) used a 0 to 100 mm VAS for assessing patient global assessment. No statistically significant differences were detected at any of the follow-up assessments: at one week post injection (WMD -15.50; 95% CI -32.32 to 1.32; P value 0.07), four weeks (WMD -12.90; 95% CI -29.51 to 3.71; P value 0.13); 12 weeks (WMD -9.20; 95% CI -24.18 to 5.78; P value 0.2), 24 weeks (WMD -3.70; 95% CI -20.47 to 13.07; P value 0.7), 52 weeks (WMD -0.40; 95% CI -9.22 to 8.42; P value 0.9), or 104 weeks post injection (WMD -1.10; 95% CI -12.00 to 9.80; P value 0.8).

Treatment preference was assessed in three trials (Dieppe 1980a; Dieppe 1980b; Jones 1996). In all three trials, IA corticosteroid was preferred over placebo, 83% versus 17% (Dieppe 1980a), 83% versus 46% (Dieppe 1980b), and 51% versus 24% (Jones 1996); RR (FE) was 2.22 (95% CI 1.57 to 3.15; P value 0.00001). This is equivalent to a risk difference of 35%, and a NNT of three.

In terms of number of patients showing improvement, a statistically significant difference was detected in favour of IA corticosteroid compared to placebo at one week post injection (Cederlof 1966; Gaffney 1995; Popov 1989); RR (FE) was 1.44 (95% CI 1.13 to 1.82; P value 0.003). This is equivalent to a risk difference of 23%, and a NNT of four. There were no significant differences detected, and no evidence of effect, from three to 24 weeks post injection. (At three weeks post injection RR was 0.91 (95% CI 0.67 to 1.24; P value 0.6) (Cederlof 1966), at six weeks RR was 1.06 (95% CI 0.86 to 1.31; P value 0.6) (Gaffney 1995; Miller 1958), at eight weeks RR was 0.86 (95% CI 0.60 to 1.23; P value 0.4) (Cederlof 1966), and at 24 weeks RR was 0.94 (95% CI 0.81 to 1.09; P value 0.4) (Miller 1958)).

Corticosteroid versus placebo: other outcome measures

There were no statistically significant differences between triamcinolone acetonide and saline for WOMAC stiffness (0 to 100 mm VAS) in the Raynauld trial (Raynauld 2003) at one year (WMD -6.70; 95% CI -19.24 to 5.84; P value 0.3), or at two years post injection (WMD -8.60; 95% CI -20.78 to 3.58; P value 0.17). The RevMan analysis differed from the original Raynauld analysis where a statistically significant difference (P value 0.0511) was reported in favour of triamcinolone acetonide in WOMAC stiffness using area under the curve of the normalized values for knee stiffness. However, when analysis of variance for repeated measurements was used, no statistically significant difference was detected at two years (P value 0.86).

There were no statistically significant differences between triamcinolone acetonide and saline for WOMAC total score (0 to 100 mm VAS) in the Raynauld trial (Raynauld 2003) at one year (WMD -7.80; 95% CI -17.19 to 1.59; P value 0.10), or at two years post injection (WMD -4.60; 95% CI -16.98 to 7.78; P value 0.5).

There were no statistically significant differences between triamcinolone acetonide and saline for joint space width (mm) in the Raynauld trial (Raynauld 2003) at one year (WMD 0.14; 95% CI -2.90 to 3.18; P value 0.9), or at two years post injection (WMD 0.16; 95% CI -2.23 to 2.55; P value 0.9).

Corticosteroid versus placebo: safety

No statistically significant differences were detected in the total number of withdrawals overall, RR was 0.60 (95% CI 0.25 to 1.45; P value 0.3) or in the number of withdrawals due to lack of efficacy, RR was 0.61 (95% CI 0.23 to 1.65; P value 0.3) (Ravaud 1999; Raynauld 2003).

No statistically significant differences were detected in the number of patients reporting post injection flare, RR was 0.80 (95% CI 0.26 to 2.48; P value 0.7) (Friedman 1980), or in the number of patients reporting local discomfort, RR was 0.45 (95% CI 0.10 to 2.11; P value 0.3) (Ravaud 1999).

Corticosteroid versus joint lavage plus intra-articular placebo: efficacy

Two trials compared IA corticosteroid and arthroscopic joint lavage (Ravaud 1999; Smith 2003).

No statistically significant differences were detected in the Ravaud trial (Ravaud 1999) for the following four outcome measures: number of responders defined as at least a 30% reduction in pain VAS from baseline; pain on a 100 mm VAS; the Lequesne Index; or in the global assessment scored on a 100 mm VAS.
The statistical values supporting these results were:

Number of responders: at one week post injection the RR was 1.34 (95% CI 0.79 to 2.30; P value 0.3), at four weeks the RR was 1.18 (95% CI 0.67 to 2.07; P value 0.6), at 12 weeks the RR was 1.09 (95% CI 0.61 to 1.96; P value 0.8), at 24 weeks the RR was 1.01 (95% CI 0.55 to 1.85; P value 1).

Pain on a 100 mm VAS: at one week post injection (WMD -12.00; 95% CI -26.66 to 2.66; P value 0.11), at four weeks (WMD -5.90; 95% CI -21.83 to 10.03; P value 0.5), at 12 weeks (WMD 4.50; 95% CI -11.34 to 20.34; P value 0.6), and at 24 weeks (WMD 3.10; 95% CI -13.48 to 19.68; P value 0.7).

Lequesne Index (0 to 24): at one week post injection (WMD -0.30; 95% CI -2.89 to 2.29; P value 0.8), at four weeks (WMD -0.90; 95% CI -1.51 to 3.51; P value 0.4), and at 24 weeks (WMD 0.60; 95% CI -2.11 to 3.31; P value 0.7).

Patient global assessment (0 to 100 mm VAS): at one week post injection (WMD -9.90; 95% CI -27.27 to 7.47; P value 0.3), at four weeks (WMD -1.10; 95% CI -18.85 to 16.65; P value 0.9), at 12 weeks (WMD 6.90; 95% CI -10.76 to 24.56; P value 0.4), and at 24 weeks post injection (WMD 8.20; 95% CI -10.22 to 26.62; P value 0.4).

In the Smith trial (Smith 2003), there was a statistically significant difference in the presence of effusion in favour of arthroscopy with methylprednisolone acetate compared to arthroscopy with saline at two weeks post injection only. There were no statistically significant differences detected at other time points, or for the outcomes of pain on movement, or the proportion of OARSI criteria responders at any follow-up point.

The statistical values supporting these results were as follows:

In the presence of effusion: at two weeks post injection RR was 0.19 (95% CI 0.04 to 0.83; P value 0.03; NNT = 5). At the four subsequent follow-up assessments there were no statistically significant differences: at four weeks RR was 0.47 (95% CI 0.20 to 1.14; P value 0.10), at eight weeks RR was 0.47 (95% CI 0.20 to 1.14; P value 0.10), at 12 weeks RR was 0.87 (95% CI 0.39 to 1.93; P value 0.7), and at 24 weeks post injection RR was 0.72 (95% CI 0.36 to 1.45; P value 0.4).

Pain on movement was measured as the number of responders (at least 30% reduction): at two weeks post injection RR was 1.25 (95% CI 0.86 to 1.83; P value 0.2), at four weeks RR was 1.14 (95% CI 0.79 to 1.66; P value 0.5), at eight weeks RR was 1.11 (95% CI 0.74 to 1.66; P value 0.6), at 12 weeks RR was 0.87 (95% CI 0.55 to 1.37; P value 0.5), and at 24 weeks post injection RR was 0.93 (95% CI 0.53 to 1.63; P value 0.8).

Proportion of OARSI criteria responders (at least 20% decrease in pain VAS and an absolute change of greater than 10 mm and/or an improvement in function of greater than 20% and an absolute change of 10 units compared with baseline): at two weeks post injection RR was 1.45 (95% CI 0.93 to 2.24; P value 0.10), at four weeks RR was 1.74 (95% CI 1.00 to 3.02; P value 0.05), at eight weeks RR was 1.66 (95% CI 0.95 to 2.91; P value 0.08), at 12 weeks RR was 1.56 (95% CI 0.84 to 2.90; P value 0.16, and at 24 weeks RR was 1.98 (95% CI 0.93 to 4.23; P value 0.08). The RevMan analysis differed from the Smith publication where a statistically significant difference was found at four weeks post injection in favour of the steroid group for this outcome (P value 0.004) using a generalized linear model with log link and binary error distribution to model the RR, and where RR was adjusted for severity of x-ray grade and baseline score.

Corticosteroid versus joint lavage plus intra-articular placebo: safety

No statistically significant differences were detected in the total withdrawals overall (Cortivazol 20% versus joint lavage 19%), RR was 1.05 (95% CI 0.32 to 3.42; P value 0.9) or in the number of withdrawals due to lack of efficacy (Cortivazol 16% versus joint lavage 19%), RR was 0.84 (95% CI 0.24 to 2.96; P value 0.8); or in the number of patients reporting local discomfort (Cortivazol 8% versus joint lavage 19%), RR was 0.42 (95% CI 0.09 to 2.07; P value 0.3) (Ravaud 1999). In the Smith trial (Smith 2003), the publication did not report group allocations for the three patients that required further sutures of arthroscopy portals.

Corticosteroid versus hyaluronan (hyaluronic acid) or hylan

Nine trials compared IA corticosteroid and hyaluronan or hylan: five with Hyalgan, two with hylan G-F 20 (Synvisc) and two with Orthovisc.

Corticosteroid versus Hyalgan: efficacy

Five RCTs compared Hyalgan and IA corticosteroid.

Four were comparisons of Hyalgan and methylprednisolone acetate (Depomedrol (MPA)) (Frizziero 2002; Leadini 1987; Leadini 1991; Pietrogrande 1991) and one a comparison of Hyalgan and triamcinolone hexacetonide (Jones 1995). There was a statistically significant difference in favour of Hyalgan for spontaneous pain intensity (0 to 100 mm VAS) at five to 13 weeks post injection (WMD -7.73; 95% CI -12.81 to -2.64; P value 0.003) (Leadini 1987; Leadini 1991; Pietrogrande 1991), when Hyalgan was 11 to 41% more effective than MPA. However, there were no statistically significant differences between one and four weeks post injection (WMD -4.90; 95% CI -9.91 to 0.10; P value 0.05) (Leadini 1987; Leadini 1991; Pietrogrande 1991), or at 45 to 52 weeks (WMD 2.50; 95% CI -14.98 to 19.98; P value 0.8) (Leadini 1987).

There was no statistically significant difference at any time point for pain expressed as the number of joints with moderate or severe pain under load (Leadini 1987): between one and four weeks post injection, RR was 1.00 (95% CI 0.47 to 2.14; P value 1), at five
to 13 weeks post injection, RR was 0.86 (95% CI 0.35 to 2.10; P value 0.7), at 45 to 52 weeks post injection, RR was 0.82 (95% CI 0.46 to 1.49; P value 0.5).

There was a statistically significant difference in favour of Hylagan for pain expressed as the number of patients with moderate/severe pain under load (Leardini 1991; Pietrogrande 1991) at five to 13 weeks post injection, RR was 0.61 (95% CI 0.44 to 0.84; P value 0.003), when the NNT was 10, but not at one to four weeks post injection, RR (RE) was 0.90 (95% CI 0.54 to 1.50; P value 0.7).

There were no statistically significant differences in the number of joints with moderate or severe walking pain detected at the three time points: one to four weeks post injection, RR was 1.22 (95% CI 0.65 to 2.29; P value 0.5), at five to 13 weeks, RR was 0.80 (95% CI 0.40 to 1.60; P value 0.5), and at 45 to 52 weeks post injection, RR was 1.04 (95% CI 0.67 to 1.60; P value 0.9) (Leardini 1987).

There was no statistically significant difference in the number of patients with moderate or greater night pain at one to four weeks post injection, RR (RE) was 1.12 (95% CI 0.66 to 2.11; P value 0.9), or at five to 13 weeks, RR was 0.14 (95% CI 0.02 to 1.13; P value 0.07) (Leardini 1991; Pietrogrande 1991).

There was a statistically significant difference in favour of Hylagan for the number of patients with moderate or greater rest pain at five to 13 weeks post injection, RR was 0.39 (95% CI 0.19 to 0.78; P value 0.008) (Leardini 1991; Pietrogrande 1991), when the NNT was 20. However, there was no statistically significant difference at one to four weeks post injection, RR was 0.68 (95% CI 0.38 to 1.24; P value 0.2).

Statistically significant differences in range of motion (flexion) in favour of Hylagan were found at one to four weeks post injection (WMD 5.93; 95% CI 0.71 to 11.14; P value 0.03), and at five to 13 weeks post injection (WMD 5.41; 95% CI 0.54 to 10.28; P value 0.03) (Leardini 1987; Pietrogrande 1991) (i.e. Hylagan was 2% more effective than MPA), but no difference was detected at 45 to 52 weeks post injection (WMD 1.50; 95% CI -12.92 to 15.92; P value 0.8) (Leardini 1987).

The global assessment, expressed by number of patients as ‘good’ or ‘very good’, showed a statistically significant difference in favour of Hylagan at five to 13 weeks post injection (WMD 1.86; 95% CI 1.26 to 2.75; P value 0.002) (Leardini 1991; Pietrogrande 1991), when the NNT for patient global assessment is seven. However there were no significant differences between the groups at one to four weeks post injection, RR (RE) was 0.98 (95% CI 0.47 to 2.06; P value 1) (Frizziero 2002; Leardini 1991; Pietrogrande 1991), or at 45 to 52 weeks (WMD 1.05; 95% CI 0.81 to 1.36; P value 0.7) (Frizziero 2002).

The RCT that compared Hylagan and triamcinolone hexacetonide (Jones 1995) showed no statistically significant differences between treatments detected by the three pain measures (100 mm VAS), except for pain at night at 14 to 26 weeks post injection (WMD -20.70; 95% CI -37.74 to -3.66; P value 0.02), when Hylagan was 26% more effective than triamcinolone hexacetonide in relieving pain. The statistical values supporting these results were as follows:

Pain on nominated activity: at 14 to 26 weeks post injection (WMD -10.00; 95% CI -31.83 to 11.83; P value 0.4), and at end of treatment (WMD -0.20; 95% CI -17.39 to 16.99; P value 1).

Pain at rest: at 14 to 26 weeks post injection (WMD -20.40; 95% CI -43.92 to 3.12; P value 0.09), and at end of treatment (WMD -0.70; 95% CI -18.17 to 16.77; P value 0.9) (the RevMan analysis differed from the original analysis by Jones (Jones 1995), which reported significant differences in favour of Hylagan in pain on nominated activity and pain at rest at 14 to 26 weeks post injection).

Pain at night: at end of treatment (WMD -7.10; 95% CI -24.30 to 10.10; P value 0.4).

Corticosteroid versus Hylagan: safety

There were no statistically significant differences in any of the extracted safety outcomes.

For the four trials comparing Hylagan and MPA, there was no difference in:

1. (1) the total number of withdrawals overall: at one to four weeks post injection, RR was 0.54 (95% CI 0.21 to 1.38; P value 0.2) (Frizziero 2002), at five to 13 weeks, RR was 3.00 (95% CI 0.13 to 71.74; P value 0.5) (Leardini 1991; Pietrogrande 1991), at 14 to 26 weeks, RR was 1.81 (95% CI 0.67 to 4.91; P value 0.2) (Frizziero 2002), or at 45 to 52 weeks, RR was 1.67 (95% CI 0.46 to 6.06; P value 0.4) (Leardini 1987);

2. (2) the number of patients withdrawn due to lack of efficacy: at five to 13 weeks post injection, RR was 3.00 (95% CI 0.13 to 71.74; P value 0.5) (Pietrogrande 1991);

3. (3) the number of joints with local reactions: at one to four weeks post injection, RR was 1.33 (95% CI 0.34 to 5.21; P value 0.7) (Leardini 1987);

4. (4) the number of patients with local or systemic reactions: at five to 13 weeks post injection, RR was 3.00 (95% CI 0.13 to 71.74; P value 0.5) (Leardini 1991; Pietrogrande 1991);

5. (5) the number of patients withdrawn due to adverse events after the first injection in the Frizziero trial (Frizziero 2002), RR was 0.30 (95% CI 0.01 to 7.24; P value 0.5).

There were no statistically significant differences between Hylagan and triamcinolone hexacetonide (Jones 1995) in

1. (1) the total number of withdrawals overall: at 14 to 26 weeks post injection RR was 0.80 (95% CI 0.56 to 1.14; P value 0.2), or at
the end of treatment, RR was 0.73 (95% CI 0.18 to 2.99; P value 0.7);

(2) the number of withdrawals due to lack of efficacy: at 14 to 26 weeks post injection RR was 0.89 (95% CI 0.49 to 1.65; P value 0.7), and at the end of treatment RR was 4.85 (95% CI 0.24 to 97.11; P value 0.3);

(3) the number of withdrawals due to adverse events: at 14 to 26 weeks post injection RR was 0.78 (95% CI 0.23 to 2.62; P value 0.7), and at the end of treatment RR was 0.97 (95% CI 0.06 to 14.82; P value 1).

**Corticosteroid versus Hylan G-F 20 (Synvisc)**

Two RCTs compared Hylan G-F 20 and IA corticosteroid.

One RCT was a comparison of Hylan G-F 20 and betamethasone sodium phosphate-betamethasone acetate (Leopold 2003; Redd 2003), the other compared Hylan G-F 20 and triamcinolone hexacetonide (Caborn 2004).

**Corticosteroid versus Hylan G-F 20 (Synvisc): efficacy**

The efficacy outcome measure results in the Leopold trial (Leopold 2003) were presented as changes in median scores because the data were not normally distributed. Therefore, efficacy data for this RCT are not reported here, though safety data are reported in the next section.

Statistically significant differences in favour of Hylan G-F 20 compared to triamcinolone hexacetonide were found for the following outcomes of efficacy in the Caborn trial (Caborn 2004):

(1) WOMAC pain walking on a flat surface (scored 0 to 4): at five to 13 weeks post injection (WMD -0.40; 95% CI -0.65 to -0.15; P value 0.002), and at 14 to 26 weeks (WMD -0.40; 95% CI -0.68 to -0.12; P value 0.005). Hylan G-F 20 was 17% more effective than triamcinolone hexacetonide;

(2) WOMAC physical function subscale (scored 0 to 68): at five to 13 weeks post injection (WMD -5.00; 95% CI -8.86 to -1.14; P value 0.01), and at 14 to 26 weeks post injection (WMD -5.20; 95% CI -9.10 to -1.30; P value 0.009). Hylan G-F 20 was, on average, 17% more effective than triamcinolone hexacetonide;

(3) WOMAC total score (scored 0 to 96): at five to 13 weeks post injection (WMD -7.40; 95% CI -12.74 to -2.06; P value 0.007), and at 14 to 26 weeks post injection (WMD -7.30; 95% CI -12.76 to -1.84; P value 0.009). Hylan G-F 20 was 15% more effective than triamcinolone hexacetonide;

(4) Patient global assessment (scored 0 to 100 mm VAS): at five to 13 weeks post injection (WMD -13.40; 95% CI -20.03 to -6.77; P value 0.00007), and at 14 to 26 weeks post injection (WMD -15.10; 95% CI -22.17 to -8.03; P value 0.00003). Hylan G-F 20 was approximately 23% more effective than triamcinolone hexacetonide.

In the Caborn trial (Caborn 2004), there was a statistically significant difference in the number of responders defined as at least a one-point improvement in the WOMAC pain walking on a flat surface in favour of Hylan G-F 20 at five to 13 weeks post injection, RR was 1.44 (95% CI 1.09 to 1.90; P value 0.01). The NNT for the number of responders was five. However, there were no significant differences at one to four weeks post injection, RR was 1.21 (95% CI 0.96 to 1.53; P value 0.11), or at 14 to 26 weeks, the RR was 1.44 (95% CI 1.00 to 2.09; P value 0.05). There was no statistically significant difference in use of analgesics up to 11 weeks post injection, RR was 1.01 (95% CI 0.97 to 1.06; P value 0.6) or from 12 to 26 weeks post injection, RR was 0.84 (95% CI 0.64 to 1.11; P value 0.2).

**Corticosteroid versus Hylan G-F 20 (Synvisc): safety**

In the Leopold trial (Leopold 2003), there were no statistically significant differences in safety outcomes: for total withdrawals overall, RR was 1.56 (95% CI 0.74 to 3.26; P value 0.2); for withdrawals due to lack of efficacy, RR was 1.50 (95% CI 0.67 to 3.35; P value 0.3); and for withdrawals due to acute local reactions, RR was 3.31 (95% CI 0.14 to 78.84; P value 0.5).

In the Caborn trial (Caborn 2004), there was a statistically significant difference in favour of Hylan G-F 20 compared to triamcinolone hexacetonide in the number of withdrawals due to lack of efficacy, RR was 0.03 (95% CI 0.00 to 0.48; P value 0.01). There were no statistically significant differences in the total number of withdrawals overall, RR was 0.78 (95% CI 0.52 to 1.17; P value 0.2), or the number of withdrawals due to adverse events, RR was 1.00 (95% CI 0.44 to 2.26; P value 1).

**Corticosteroid versus Orthovisc: efficacy**

Two trials compared Orthovisc with different IA corticosteroids: betamethasone (Tēkeoglu 1998), and 6-methylprednisolone acetate (6-MPA) (Tascioglu 2003).

At five to 13 weeks post injection in the Orthovisc/betamethasone trial (Tēkeoglu 1998), Orthovisc was significantly better than betamethasone for:

(1) WOMAC function (WMD -9.00; 95% CI -14.15 to -3.85; P value 0.0006), where Orthovisc was 20% more effective than betamethasone in improving physical function;

(2) Patient global assessment (i.e. number of patients 'good/very good'), RR was 1.88 (95% CI 1.04 to 3.39; P value 0.04). The NNT is three.

However, at one to four weeks post injection there were no statistically significant differences for:

(1) WOMAC function (scored 17 to 85) (WMD 3.00; 95% CI -2.39 to 8.39; P value 0.3);

(2) the number of patients classified as ‘good’ or ‘very good’, RR was 0.83 (95% CI 0.47 to 1.47; P value 0.5); and,
(3) maximum flexion (WMD -4.90; 95% CI -14.69 to 4.89; P value 0.3). There was also no between-group difference for maximum flexion at five to 13 weeks (WMD -7.05; 95% CI -15.48 to 1.38; P value 0.10).

In the Orthovisc/6-methylprednisolone acetate (6-MPA) trial (Tascioglu 2003) statistically significant differences in favour of the Orthovisc group were detected in all pain outcomes and the Lequesne Index at five to 13 weeks post injection:

(1) pain on weight bearing (WMD -15.64; 95% CI -24.51 to -6.77; P value 0.0006);
(2) pain at rest (WMD -7.70; 95% CI -13.50 to -1.90; P value 0.009);
(3) pain on walking (WMD -18.43; 95% CI -29.19 to -7.67; P value 0.0008); and
(4) Lequesne Index (WMD -1.40; 95% CI -2.13 to -0.67; P value 0.0002).

Orthovisc was between 25% and 32% more effective than 6-MPA in relieving pain, and 18% more effective than 6-MPA in improving function (Lequesne). However, at one to four weeks post injection, there were no statistically significant differences between the two groups for any of the pain outcome measures, the Lequesne Index or flexion outcome measures, or for the latter at five to 13 weeks (WMD 2.36; 95% CI -1.82 to 6.54; P value 0.3).

At 14 to 26 weeks post injection, statistically significant differences in all outcome measures, except pain on rest, were detected in favour of the Orthovisc group:

(1) pain on weight bearing (WMD -15.40; 95% CI -25.91 to -4.89; P value 0.004);
(2) pain on walking (WMD -14.90; 95% CI -25.91 to -3.89; P value 0.008);
(3) Lequesne Index (WMD -1.14; 95% CI -2.16 to -0.12; P value 0.03);
(4) flexion (WMD 5.00; 95% CI 0.19 to 9.81; P value 0.04); and
(5) pain at rest (WMD -2.90; 95% CI -9.47 to 3.67; P value 0.4).

Orthovisc was between 20% and 31% more effective than 6-MPA in relieving pain, and between 4% and 15% more effective in improving function.

The RevMan analysis differed from the analysis in the original trial report (Tascioglu 2003), by detecting previously unreported statistically significant differences in favour of Orthovisc between the groups at six months for pain on weight bearing (P value 0.004), pain on walking (P value 0.008), Lequesne Index (P value 0.03), and flexion (P value 0.04).

Corticosteroid versus Orthovisc: safety

There were no adverse local (e.g. post-injection synovitis) or systemic reactions reported in either the Orthovisc or betamethasone group with all patients completing the Tekeoglue trial (Tekeoglue 1998), and no statistically significant differences in the safety profile of Orthovisc compared to 6-MPA in the Tascioglu trial (Tascioglu 2003).

In the Tascioglu trial one patient in each group withdrew due to increased pain, RR was 1.00 (95% CI 0.07 to 15.26; P value 1), and a similar number of patients:

(1) were withdrawn overall: Orthovisc 6.7% and 6-MPA 10%, RR was 0.67 (95% CI 0.12 to 3.71; P value 0.6);
(2) reported musculoskeletal adverse events: Orthovisc 25% and 6-MPA 19%, RR was 1.35 (95% CI 0.49 to 3.74; P value 0.6);
(3) reported adverse skin events: Orthovisc 7% and 6-MPA 4%, RR was 1.93 (95% CI 0.19 to 20.05; P value 0.6);
(4) reported gastrointestinal adverse events: Orthovisc 11% and 6-MPA 4%, RR was 2.62 (95% CI 0.26 to 25.7; P value 0.7);
(5) reported general adverse events: Orthovisc 14% and 6-MPA 19%, RR was 0.77 (95% CI 0.23 to 2.57; P value 0.7);
(6) reported knee pain after injection: Orthovisc 21% and 6-MPA 19%, RR was 1.16 (95% CI 0.40 to 3.35; P value 0.8).

Corticosteroid versus corticosteroid

Six trials compared different IA corticosteroids against each other (Bias 2001; Popov 1989; Pyne 2004; Thorpe 1985; Valtonen 1981; Wright 1960).

Corticosteroid versus corticosteroid: pain

Three of the six trials comparing one corticosteroid against another included pain data that could be used in this review (Bias 2001; Valtonen 1981; Wright 1960).

In the Valtonen trial (Valtonen 1981), a statistically significant difference was detected in the number of patients reporting pain reduction in favour of triamcinolone hexacetonide compared to betamethasone at one week post injection (76% versus 43%; RR was 1.78 (95% CI 1.03 to 3.08; P value 0.04)), two weeks (86% versus 48%; RR was 1.80 (95% CI 1.11 to 2.91; P value 0.02)), and four weeks (76% versus 38%; RR was 2.00 (95% CI 1.10 to 3.63; P value 0.02)). The NNT with triamcinolone hexacetonide versus betamethasone to achieve an improvement was three.

In the Wright trial (Wright 1960), no statistically significant difference was detected in the number of knees that improved by two weeks post injection (hydrocortisone tertiary-butylacetate (50%) RR was 1.32 (95% CI 0.89 to 1.95; P value 0.17)).

In the Bias trial (Bias 2001), which compared different doses of dexamethasone palmitate (4 mg versus 12 mg), there were no statistically significant differences detected in any pain outcomes.
Corticosteroid versus corticosteroid: function

Only one of the six trials comparing one corticosteroid against another included data on function that could be used in this review (Valtonen 1981). It detected no statistically significant difference in flexion at four weeks post injection (WMD 0; 95% CI -9.09 to 9.09; P value 1).

Corticosteroid versus corticosteroid: global assessment

Four of the six trials comparing one corticosteroid against another included global assessment data that could be used in this review (Popov 1989; Pyne 2004; Thorpe 1985; Valtonen 1981). None of them showed any statistically significant differences between treatments for the number of:

1. Pain during movement (0 to 3) at one week post injection (WMD -0.20; 95% CI -0.99 to 0.59; P value 0.6), two weeks (WMD 0.10; 95% CI -0.43 to 0.63; P value 0.7), three weeks (WMD 0.40; 95% CI -0.34 to 1.14; P value 0.3), or four weeks (WMD 0.20; 95% CI -0.52 to 0.92; P value 0.6);

2. Pain at rest (0 to 3) at one week post injection (WMD -0.60; 95% CI -1.37 to 0.17; P value 0.13), two weeks (WMD -0.20; 95% CI -0.53 to 0.13; P value 0.2), three weeks (WMD 0; 95% CI -0.44 to 0.44; P value 1), or four weeks (WMD -0.20; 95% CI -0.63 to 0.23; P value 0.4);

3. Pain on pressure (0 to 3) at one week post injection (WMD -0.50; 95% CI -1.13 to 0.13; P value 0.12), two weeks (WMD 0; 95% CI -0.40 to 0.40; P value 1), three weeks (WMD -0.10; 95% CI -0.59 to 0.39; P value 0.7), or four weeks (WMD 0.20; 95% CI -0.36 to 0.76; P value 0.5).

Corticosteroid versus corticosteroid: safety

None of the six trials comparing one corticosteroid against another included data on safety that could be used in this review (Popov 1989; Pyne 2004; Thorpe 1985; Valtonen 1981). Therefore, it appears that the beneficial effects of IA corticosteroids was more effective than placebo in pain reduction, but a lack of evidence for benefit in functional improvement. From four to 24 weeks post injection, there was no compelling evidence of benefit, although some mid and late stage benefit in favour of corticosteroids was noted. Therefore, it appears that the beneficial effects of IA corticosteroids are rapid in onset, but may be relatively short lived (approximately one to three weeks). In contrast, the beneficial effects of the HA products (Hyalgan, Hylan G-F 20 and Orthovisc) are of similar or slower onset, but are more durable, with clinical benefit being detected at five to 13 weeks post injection.

Compared to other pharmacological treatments for OA, e.g. NSAIDs, very few randomised, controlled trials have been published comparing different IA corticosteroids. In the comparisons between IA corticosteroid preparations, only one study detected a statistically significant difference in reduction of pain, and favoured triamcinolone hexacetonide over betamethasone. No other differences were detected in any of the efficacy or safety outcome measures. Given the relative paucity of head-to-head studies of IA corticosteroid preparations, the results of our analyses do not permit broad generalisation.

In the comparisons between IA corticosteroid (Cortizanol) and joint lavage, no differences were detected in any of the efficacy or safety outcome measures.

Corticosteroid versus corticosteroid: other outcome measures

In the Bias trial (Bias 2001), which compared different doses of dexamethasone palmitate (4 mg versus 12 mg), no statistically significant differences were detected in the activity index to assess the degree of inflammation (scored 0 to 10: based on pain, temperature, effusion, swelling) at one week post injection (WMD 0.60; 95% CI -0.69 to 0.49; P value 0.3), two weeks (WMD -0.40; 95% CI -1.48 to 0.68; P value 0.3), three weeks (WMD -0.10; 95% CI -1.28 to 1.08; P value 0.9), or four weeks (WMD -0.40; 95% CI -1.77 to 0.97; P value 0.6).

Corticosteroid versus corticosteroid: other outcome measures

In the Bias trial (Bias 2001), which compared different doses of dexamethasone palmitate (4 mg versus 12 mg), no statistically significant differences were detected in the activity index to assess the degree of inflammation (scored 0 to 10: based on pain, temperature, effusion, swelling) at one week post injection (WMD 0.60; 95% CI -0.69 to 0.49; P value 0.3), two weeks (WMD -0.40; 95% CI -1.48 to 0.68; P value 0.3), three weeks (WMD -0.10; 95% CI -1.28 to 1.08; P value 0.9), or four weeks (WMD -0.40; 95% CI -1.77 to 0.97; P value 0.6).
safety outcome measures.

The explanation for the variability in response to IA corticosteroids is contentious. Jones suggested that it could be partly attributable to inaccurate injection (Jones 1993). He showed that the placement of IA injections is often inaccurate, which may contribute to the incidence of local tissue damage (atrophy of soft tissue and fat). Gaffney (Gaffney 1995) suggested that the accuracy of injection could relate to the association between pain relief and the successful aspiration of synovial fluid.

A mail survey of rheumatologists in New South Wales showed wide variation in aseptic techniques and number of weekly injections (Lawford 1994). This survey also reported a wide variety of soft tissue complications, e.g. tendon rupture, soft tissue infection, neuropraxia (a condition in which after injury a nerve remains in place but does not transmit electrical impulses), and subcutaneous skin atrophy (wasting away of tissue). Bliddal proposed mini arthrography as a means of quality assurance in studies involving IA injections (Bliddal 1999). The use of ultrasound to guide IA injections has also been investigated (Brown 2001; Fredberg 2001; Qvistgaard 2001). In a double-blind randomised study, Sambrook (Sambrook 1989) compared a peripatellar (around the kneecap) route of injection to a more standard IA route using methylprednisolone in 38 patients with knee OA. They concluded that peripatellar injection was at least as useful as the standard IA injection technique. Recognizing the importance of joint aspiration and injection, Sack published a how-to-guide (Sack 1999) and more recently Schumacher a review on aspiration and injection therapies for joints (Schumacher 2003).

Clinical improvement may be due to treatment effect, reflect spontaneous improvement (Ravaud 1999), or natural remission during the course of the trial (Popov 1989). Jones (Jones 1996) found no predictors of response; and response was not confined to those with clinical evidence of inflammation. It has been suggested that there are subgroups of people who do, and do not, respond. Dieppe (Dieppe 1980a; Dieppe 1980b) queried whether different types of OA respond differently to IA steroid therapy. He found no obvious correlations with clinical, radiological or synovial fluid findings except for positive results occurring in all those with chondrocalcinosis (calcium pyrophosphate crystals present in joint cartilage). Gaffney (Gaffney 1995) questioned whether the clinical response was related more to injection accuracy than the response of a subgroup. His subgroup analysis of triamcinolone hexacetonide-treated patients revealed that improvement for pain (on VAS) was greater among patients with clinical evidence of joint effusion and those who had synovial fluid successfully aspirated at time of injection. In contrast, Jones (Jones 1996) found that synovial fluid aspiration did not predict clinical response.

This review cannot evaluate any dose-response relationship with the different corticosteroid preparations. All the included trials used a fixed dose in their design. However, a number of observations are worth noting. Miller (Miller 1958) could not attribute any effect produced to the volume of fluid injected. Popov (Popov 1989) recommended hydrocortisone acetate as the drug of choice as his studies showed equal efficacy of low dose hydrocortisone acetate (50 mg) with more than average triamcinolone acetonide doses. Thorpe’s trial (Thorpe 1985) results showed that smaller doses of triamcinolone acetonide may be more effective than methylprednisolone acetate, with 10 mg of triamcinolone acetonide being equivalent to 40 mg methylprednisolone acetate. Valtonen (Valtonen 1981) reported that the duration of effect of triamcinolone was substantially longer than that of betamethasone. No statistically significant difference was reported between hydrocortisone acetate and hydrocortisone tertiary-butyrate (Wright 1960).

A mail survey of members of the American College of Rheumatology (ACR) indicated that the corticosteroids favoured by the respondents depended upon place of training: methylprednisolone acetate was preferred by those trained in the eastern United States, triamcinolone hexacetonide by those trained in the Midwest and Southwest, and triamcinolone acetonide by those trained in the West (Centeno 1994). Only triamcinolone hexacetonide was chosen primarily because of efficacy. Respondents used 1 ml of steroid combined with local anaesthetic. Twenty-nine percent did not restrict weight bearing while 8% recommended limited weight bearing for one week or more post injection.

The results of a British mail survey of consultant rheumatologists showed wide divergence regarding personal and patient preparation before IA injections (Haslock 1995). Approximately 25% used no local anaesthetic. Most advised rest or reduced use of weight-bearing joints for 24 to 48 hours post injection. Concern has been raised that repeated IA corticosteroid injections might cause progressive cartilage damage. Lane (Lane 1997) recommended that IA corticosteroid injections should not be given in a single joint at more than three monthly intervals. Similarly, Ratiner (Ratiner 2001) recommended that there should be no more than two to three injections per joint per year in routine cases.

It has been suggested that the short term benefits of reduced pain and inflammation have to be weighed against possible adverse effects concerning the “articular cartilage, the synovium and the host immune response” (Gosal 1999). Albeit uncommon, complications of IA corticosteroids include the following: post injection flare (reddening of the skin), crystal-induced synovitis (inflammation of joint membranes), tissue atrophy (wasting of tissue), fat necrosis, calcification (deposition of calcium salts in tissue), sepsis (tissue destruction by bacteria or their toxins), steroid arthropathy (acceleration of cartilage damage), vascular necrosis (death of blood vessels), and haematoma (swelling caused by accumulation of blood) (Ayral 2001; Lawford 1994; McColl 2000; Noordlinger 2001; Ratiner 2001; Rozental 2000; Seror 1999; Wada 1993). Rarely, absorption of IA corticosteroid from the joint through the body may result in fluid retention, hyperglycaemia (too much glu-
function and total WOMAC score, but not at one to four weeks. This difference is probably due to the quick onset, but often relatively short duration, of the response to IA corticosteroid treatment. Overall, these analyses suggest that Hylan G-F 20, with its longer duration of action, is as beneficial as IA corticosteroid, notwithstanding the latter's faster onset of action. Analyses of safety data also supported the safety of Hylan G-F 20, with no statistically significant differences from IA corticosteroid being detected in the majority of safety variables.

Comparative studies of IA corticosteroid against Orthovisc suggest that Orthovisc is superior to 6-MPA (Tascioglu 2003) at five to 13 weeks, and 14 to 26 weeks post-injection, and superior to betamethasone (Tekeoglu 1998) at five to 13 weeks post-injection. No statistically significant differences were detected at one to four weeks against either corticosteroid. This time-dependent difference is probably due to the quick onset, but often relatively short duration, of the response to IA corticosteroid treatment. Overall, these analyses suggest that Orthovisc, with its longer duration of action, is as beneficial as IA corticosteroids at one to four weeks, and superior at five to 13 weeks and 14 to 26 weeks, notwithstanding the latter's faster onset of action. Analyses of safety data also support the safety of Orthovisc, with no statistically significant differences of either IA corticosteroid preparation detected in the safety profile.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

In the comparisons between intra-articular (IA) corticosteroid and IA placebo, some evidence for efficacy was detected for pain and patient global assessment, at one week post injection, with evidence also for continuing efficacy at two and three weeks post-injection. Thereafter, there is diminishing evidence for efficacy, partly due to an absence of data, and partly to an inability to detect statistically significant differences in longer term follow-up. There seem to be beneficial effects on pain and patient global assessment, but little or no effect (versus placebo) on function. There is justification, therefore, for the use of IA corticosteroid therapy in selected patients with osteoarthritis of the knee (OA knee). In contrast the effect of Hyaluronic acid or hylan (HA) products on OA knee, while slower in onset, appear to be more durable than IA corticosteroids. Therefore, clinicians have therapeutic options for IA therapy, and need to choose between IA corticosteroids and HA products. In cases where there are obvious signs of inflammation, a corticosteroid preparation may offer opportunity for relief of inflammation and short term pain relief, while, in other cases, HA products (Hylan G-F 20, Hylan, Orthovisc) may offer a longer more durable response with improvement in pain, function and patient global assessment than IA corticosteroids provide.
Our analyses do not permit us to differentiate between corticosteroid products. Triamcinolone hexacetonide was superior to betamethasone for the number of patients reporting pain reduction up to four weeks post injection, but no other clinically or statistically important differences were detected in comparisons of different corticosteroid products.

Overall the analyses suggest that several IA corticosteroid preparations are efficacious in short term symptomatic treatment of OA knee. Their onset of action is fast, with effects on pain detectable at one week post-injection, and lasting for two to three weeks. Some patients experience more dramatic and prolonged symptom relief than others. The basis for this variability in response requires further study.

Implications for research

The usefulness of trials of IA corticosteroid in patients with OA of the knee has been restricted through the lack of standardisation of outcome assessments, variable assessment times, and durations. Standardisation of outcome measurement procedures would facilitate inter-trial comparisons, while trials of longer duration (e.g. greater than one month), examining different patient subgroups, and following robust guidelines for trial conduct and design would be valuable. Clinical predictors of response should be further investigated, in particular those associated with inflammation and structural damage.

ACKNOWLEDGEMENTS

The authors are grateful to Jessie McGowan for conducting the search strategy. We acknowledge the assistance of the former Musculoskeletal Review Group Co-ordinator, Maria Judd, and current Co-ordinator, Lara Maxwell, for their guidance in completing this review. The authors acknowledge Dr Alex Klestov for his translation of the Popov trial. The authors thank the two external reviewers and the consumer reviewer for their comments.

REFERENCES

References to studies included in this review

Bias 2001 [published data only]

Caborn 2004 [published data only]

Cederlof 1966 [published data only]

Dieppe 1980a [published data only]

Dieppe 1980b [published data only]

Friedman 1980 [published data only]

Gaffney 1995 [published data only]

Jones 1995 [published data only]

Jones 1996 [published data only]

Leardini 1987 [published data only]

Leardini 1991 [published data only]
Leardini G, Mattara L, Franceschini M, Perbellini A. [Intra–articular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and...
References to studies excluded from this review

Astorga 1967

Baker 1969

Cats 1979

George 1993

Jalava 1980

Jalava 1982
Intraarticular corticosteroid for treatment of osteoarthritis of the knee (Review)

Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

References to studies awaiting assessment

Gur 2001

Kim 2000

McCaffrey 2003
McCaffrey M. [A blinded randomized controlled trial of two corticosteroid preparations for the intraarticular treatment of osteoarthritis of the knee]. Presentation at Surgical Residents’ Research Day, Memorial University of Newfoundland, Canada 2003.

Additional references

ACR 2000

Altman 1986

Altman 1991

Altman 1996

Arroll 2004

Ayral 2001

Bellamy 1988
Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients
Intraarticular corticosteroid for treatment of osteoarthritis of the knee (Review)

Gosal 1999

Gosal 2000

Gossec 2004

Harauzi 2002

Haslock 1995

Hedges 1985

Helfet 1974

Hochberg 1995

Hollander 1953

Jadad 1996

Jones 1993

Kirwan 1997

Kirwan 2001
Intraarticular corticosteroid for treatment of osteoarthritis of the knee (Review)

Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
SOURCES OF SUPPORT

External sources of support
• Genzyme Biosurgery (formerly Biomatrix Inc.) and Wyeth-Ayerst provided an unrestricted educational grant CANADA

Internal sources of support
• Centre of National Research on Disability and Rehabilitation Medicine (CONROD) AUSTRALIA

INDEX TERMS

Medical Subject Headings (MeSH)
Adrenal Cortex Hormones [*administration & dosage]; Injections, Intra-Articular; Osteoarthritis, Knee [*drug therapy]; Randomized Controlled Trials

MeSH check words
Humans