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Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis.
Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD000189.
DOI: 10.1002/14651858.CD000189.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis

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Editorial group: Cochrane Musculoskeletal Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Gøtzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD000189. DOI: 10.1002/14651858.CD000189.pub2.

ABSTRACT

Background

The effect of low dose corticosteroids, equivalent to 15 mg prednisolone daily or less, in patients with rheumatoid arthritis has been questioned. We reviewed the trials that compared corticosteroids with placebo or non-steroidal, anti-inflammatory drugs.

Objectives

To determine whether short-term (i.e. as recorded within the first month of therapy), oral low-dose corticosteroids (corresponding to a maximum of 15 mg prednisolone daily) is superior to placebo and non-steroidal, anti-inflammatory drugs in patients with rheumatoid arthritis.

Search methods

PubMed, the Cochrane Central Register of Controlled Trials, reference lists and a personal archive. Date of last search Nov 2007.

Selection criteria

All randomised trials comparing an oral corticosteroid (not exceeding an equivalent of 15 mg prednisolone daily) with placebo or a non-steroidal, anti-inflammatory drug were eligible if they reported clinical outcomes within one month after start of therapy. For adverse effects, long-term trials were also selected.

Data collection and analysis

Decisions on which trials to include were made independently by two observers based on the methods sections of the trials. Standardised mean difference (random effects model) was used for the statistical analyses.

Main results

Eleven trials, involving 462 patients, were included. Two placebo-controlled trials had adequate allocation concealment. For joint tenderness, the standardised mean difference was -0.52, 95% confidence interval (CI) -1.01 to -0.03, for pain it was -0.67, 95% CI -1.58 to 0.23, and for grip strength, 0.22, 95% CI -0.40 to 0.84. The estimates for the other trials were considerably larger.

Prednisolone also had a greater effect than non-steroidal, anti-inflammatory drugs on joint tenderness (-0.63, 95% CI -1.16 to -0.11) and pain (-1.25, 95% CI -2.24 to -0.26), whereas the difference in grip strength was not significant (0.31, 95% CI -0.02 to 0.64). The main harms in long-term treatment were vertebral fractures and infections.

Authors' conclusions

Prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means. The risk of harms needs to be considered, however, especially the risk of fractures and infections. Since prednisolone is highly effective, short-term placebo controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary.

PLAIN LANGUAGE SUMMARY

Corticosteroids versus placebo and NSAIDs for rheumatoid arthritis

Short-term low-dose corticosteroids compared with placebo and nonsteroidal antiinflammatory drugs in patients with rheumatoid arthritis

Corticosteroid drugs can relieve inflammation, and in high doses they have a dramatic effect on the symptoms of rheumatoid arthritis. They are used only temporarily, however, because of serious adverse effects during long-term use. The review found that corticosteroids in low doses are very effective. They are more effective than usual anti-arthritis medications (non-steroidal anti-inflammatory drugs, or NSAIDs). The risk of harms needs to be considered, however, especially the risk of fractures and infections.

BACKGROUND

Corticosteroids were first shown to be effective in patients with rheumatoid arthritis in an uncontrolled study (Hench 1949). In 1959, a two-year randomised trial showed that an initial dose of prednisolone 20 mg daily was significantly superior to aspirin 6 g daily (Joint Committee 1959). Important harms were also noted, however, and the authors concluded that the highest acceptable dose for long-term therapy is probably in the region of 10 mg daily.

Corticosteroids have received renewed interest in recent years because of their possible beneficial effect on radiological progression (Weiss 1989). Tendencies towards such an effect have been noted both in the early trials and in a more recent report (Kirwan 1995) and will be examined in a Cochrane review (Kirwan 2007).

These findings are interesting, but oral corticosteroids are still being used mainly in high doses for their symptomatic effect, for example for acute exacerbations of rheumatoid arthritis and as "bridge therapy", before slow-acting drugs have taken effect (Harris 1983). The effect of low doses has been variable, and was questioned as late as in 1995 when the most recent trial of low-dose steroids was published (van Gestel 1995). We performed a systematic review of randomised trials which compared corticosteroids, given at a dose equivalent to no more than 15 mg prednisolone daily, with placebo or with non-steroidal, anti-inflammatory drugs. Our review is limited to the short-term effect, i.e. as recorded within the first month of therapy. However, in an analysis of the harms of steroids we also included long-term trials.

OBJECTIVES

To compare the short-term beneficial and harmful effects, i.e. as recorded within the first month of therapy, of oral low-dose corticosteroids with that of placebo and non-steroidal, anti-inflammatory drugs in patients with rheumatoid arthritis.

To compare the harms in long-term trials of oral low-dose corticosteroids with that of placebo and non-steroidal, anti-inflammatory drugs.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing an oral corticosteroid with placebo or a non-steroidal, anti-inflammatory drug in patients with rheumatoid arthritis were eligible if they reported clinical outcomes within one month after start of therapy. When there were data from several visits, the data which came closest to one week of therapy was used for the analyses. We excluded studies with high-dose steroids (exceeding an equivalent of 15 mg prednisolone daily); studies of combination therapies, for instance of a steroid and a non-steroidal, anti-inflammatory drug, and studies using quasi-randomisation methods, such as allocation by date of admission or by toss of a coin (no such studies were found).

To study the harms in more detail, we also identified moderate- and long-term randomised trials, which had compared low-dose steroids with placebo or a non-steroidal, anti-inflammatory drug.

Types of participants

Patients with rheumatoid arthritis, in all but one study defined by the criteria of the American Rheumatism Association (Arnett 1988) (the criteria have changed slightly over the years).

Types of interventions

Experimental: oral low-dose corticosteroids (not exceeding an equivalent of 15 mg prednisolone daily).
Control: placebo or oral non-steroidal, anti-inflammatory drugs.

Types of outcome measures

Joint tenderness (usually Ritchie's joint index), pain, grip strength.

Search methods for identification of studies

PubMed was searched from 1966 to November 2007: "Arthritis, Rheumatoid"[mh] AND placebo AND "Glucocorticoids"[Pharmacological Action].
The Cochrane Central Register of Controlled Trials was searched in November 2007: (glucocorticoids explode all trees (MeSH) and (Arthritis, Rheumatoid explode all trees (MeSH)) and placebo. The reference lists were scanned for additional trials and an archive in possession of one of the authors was scanned. Since most of the retrieved trials were very old and the steroid drugs were non-proprietary ones, authors and companies were not asked about possible unpublished studies.

Data collection and analysis

Decisions on which trials to include were taken independently by two observers based on the methods sections of the trials; disagreements were resolved by discussion. Details on the nature and dosage of treatments, number of randomised patients, the randomisation and blinding procedures, and exclusions after randomisation were noted. Since the outcomes were measured on different scales, even when they referred to the same quality, e.g. tender joints, we calculated the standardised mean difference. With this method, the difference in effect between two treatments is divided by the standard deviation of the measurements. By that transformation, the effect measures become dimension-less and outcomes from trials which have used different scales may therefore often be combined. As an example, the tender joint count may be recorded either as the number of tender joints or as Ritchie's index in which each joint is scored on a scale from zero to three for pain on firm palpation, and the scores are added. If the patients have very severe disease, Ritchie's index may be higher, but the standard deviation will then also be higher, and by dividing the counts with their standard deviations, the effect sizes will be of the same magnitude.

The random effects model was used since there was substantial heterogeneity. As the trials were all small, this would not be expected to lead to overestimation of treatment effects. Since data from crossover trials were only reported in summary form, as if they had been generated from a group comparative trial, we analysed them accordingly. We therefore assumed that no important carry-over effects had occurred.

RESULTS

Description of studies

Thirty-five randomised trials were initially identified, several of which had been published more than once. Twenty-four trials were excluded for various reasons. Eleven trials did not fulfil the inclusion criteria for the meta-analysis: one was not randomised although so labelled in PubMed (Hantzschel 1976), five had studied combination drugs (Badia Flores 1969; Gum 1966; Jick 1965; Siegmeth 1974; Zuckner 1969), three used too high dose (Hansen 1999; Joint Committee 1954; Joint Committee 1959), in one, 4 mg methylprednisolone was given to all the patients in the placebo group (Slonim 1969), and one concerned patients with juvenile rheumatoid arthritis (Kvien 1982) (this trial found prednisolone to be significantly better than placebo). The other 15 excluded studies were potentially eligible for the review. However, one was a five-way crossover trial (Deodhar 1973) with a grossly unbalanced design; for instance, placebo was given to 9, 13, 3, 6, and 6 patients during weeks 1, 2, 3, 4, and 5, respectively. Because of the regression towards the mean effect, we found it inappropriate to include this trial. Another trial was also unbalanced, since the steroid group was kept mobile whereas the control group received bed rest and splints for the inflamed joints (Million 1984). Two trials were too poorly reported to be usable (Fearnley 1966; Murthy 1978), and one only reported on joint size (Webb 1973). Three of these trials found prednisolone or prednisone to be significantly more effective than placebo, and one compared prednisolone and indomethacin and gave no numerical data but just reported that there was "no significant difference in response" (Murthy 1978). The eight other excluded trials were long-term studies that did not report short-term data as well (Capell 2004; Chamberlain 1976; Empire Rheum 1955; van Everdingen 2002; Harris 1983; Kirwan 1995; Leszczynski 2000; Rau 2000).

Eleven trials, involving 462 patients, were included in the review. Most of the trials were quite old and rather small. In all but one (Böhm 1967), the criteria of the American Rheumatism Association for classical or definite rheumatoid arthritis (Arnett 1988) were fulfilled. Age, proportion of females and disease duration were only reported in about half of the trials but they were typical for studies in rheumatoid arthritis. As would be expected for patients becoming enrolled in steroid trials, the severity of the disease, expressed as number of tender joints or Ritchie's tender joint index, was quite pronounced (see graphs). Prednisolone was used in seven trials and prednisone in four. Since prednisone is equipotent with prednisolone and is a pro-drug to prednisolone, we will refer to "prednisolone" as a general term in the following. The doses were 2.5-7.5 mg in four studies, 10 mg in three studies, and 15 mg in four. Data were available after one week for all studies but two for which two-week and four-week data (as two-week data were difficult to read on the graphs (Kirwan 2004)) were used, respectively.

Risk of bias in included studies

The randomisation method was only described in one of the trial reports (Kirwan 2004) but details were obtained from the authors of another study (van Gestel 1995); the treatment allocation appeared to have been adequately concealed in these two studies. All studies were double-blind apart from a single-blind study in which the patients appeared to have been blinded (Lee 1973b). Eight of the studies were of a crossover design but only one of them reported to have tested for sequence effects (Stenberg 1992). Apart from one study (Stenberg 1992), the tender joint count was recorded as Ritchie's index; pain was recorded on a ranking scale with 4 or 5 classes in two studies (Böhm 1967; Lee 1973b), on a visual analogue scale in three studies (Berry 1974; Kirwan 2004; van Gestel 1995), and as a composite pain index in two studies (Jasani 1968; Stenberg 1992).

Effects of interventions

Eleven trials, involving 462 patients were included. The results are shown in the graphs. It should be noted that if prednisolone is better than control, the standardised mean difference is negative for joint tenderness and pain, but positive for grip strength. There was large heterogeneity in the effects, and the results should therefore be interpreted with caution.

Two placebo-controlled trials had adequate allocation concealment. For joint tenderness, the standardised mean difference was -0.52, 95% confidence interval (CI) -1.01 to -0.03, for pain it was -0.67, 95% CI -1.58 to 0.23, and for grip strength, 0.22, -95% CI 0.40 to 0.84. The estimates for the other trials were considerably larger.

Prednisolone also had a greater effect than non-steroidal, anti-inflammatory drugs on joint tenderness (-0.63, 95% CI -1.16 to -0.11) and pain (-1.25, 95% CI -2.24 to -0.26), whereas the difference in grip strength was not significant (0.31, 95% CI -0.02 to 0.64).

The harms were poorly described. Five of the eleven studies we included for efficacy analyses did not report any data on harms; one study reported that no side effects occurred (Jasani 1968); two patients on prednisone had "subjective reactions" in one study (Boardman 1967); and one patient developed acute psychosis while on prednisone in one study (Lee 1973b). The three remaining studies were moderate-term studies from which we extracted short-term efficacy data (Kirwan 2004; Stenberg 1992; van Gestel 1995) and moderate- term adverse effects.

We found 12 moderate- and long-term randomised trials which had compared low-dose steroids with placebo or a non-steroidal, anti-inflammatory drug (Table 1). Because of differences in evaluation of harms and in reporting them, we did not try to pool these data. In five of the trials (203 vs 202 patients), where X-ray had been used to detect vertebral fractures, nine fractures on corticosteroids and four on placebo were reported. The incidence of infections was also increased with corticosteroids (for other reported harms, see Table 1).

DISCUSSION

Low-dose prednisolone is not only highly effective for short-term therapy, but also significantly more effective than non-steroidal, anti-inflammatory drugs. A systematic review of the effect of low-dose prednisolone after six months also found a significantly better effect of drug than of placebo (Criswell 1998).

The point estimate for the difference in effect between prednisolone and non-steroidal, anti-inflammatory drugs on grip strength was 12 mm Hg, which is the same as the point estimate for the difference in effect between non-steroidal, anti-inflammatory drugs and placebo (Gøtzsche 1989b). It is not surprising that the difference in grip strength between prednisolone and non-steroidal, anti-inflammatory drugs was not statistically significant,

since this effect measure is considerably less sensitive to drug effects than pain and joint tenderness (Gøtzsche 1990a).

There was substantial heterogeneity between the trials. Our attempts to explain its causes have been rather unsuccessful. Since most of the studies were performed decades ago, earlier trials could have overestimated the effect, for instance because of insufficiently concealed randomisation methods (Schulz 1995). However, the methodological quality of the trials was rather similar in the whole time span of 40 years and it was also similar to the quality of comparative drug trials of non-steroidal, anti-inflammatory (Gøtzsche 1989a). In accordance with this, there were no time trends for the differences in joint tenderness and pain between prednisolone and placebo (see graphs). Blinding did not seem to have been important for the heterogeneity. Only one trial was not double-blind and this trial did not yield larger effect estimates than the other trials.

Small trials may exaggerate the effect because of publication bias (Dickersin 1993; Stern 1997) and other biases. The trials were all rather small, but the effect was so pronounced that it would have been unreasonable to plan large, confirmatory trials. In this respect , steroid trials resemble trials of non-steroidal, anti-inflammatory drugs which have been shown to be effective in small crossover trials against placebo (Gøtzsche 1990a).

A possible cause for the heterogeneity could be varying degrees of concomitant therapy. Although sometimes prohibited in trial protocols, it may be difficult to ensure that patients do not take additional drugs. Since there was very sparse information on drug intake in the reports, this possibility could not be evaluated.

Another source of heterogeneity could be the use of different measurement scales. Pain, for example, was measured on three different types of scales. They were all ranking scales, and we would therefore have preferred to analyse pain with rank sum tests, or as binary data after reduction of the level of measurement. Since the original authors had used parametric statistics, we decided to do so as well, rather than discard the data.

There was no clear relation between dose and effect despite the fact that the doses varied from 2.5 mg to 15 mg daily. It was not the aim of our review, however, to study dose-response relationships which are elucidated more reliably in studies where patients are randomised to different doses. A remarkable effect was seen in a study in which the average dose was only 3 mg daily but where the patients were allowed to start on 7.5 mg when they experienced flares of the arthritis and were advised to take nothing when they were well (Stenberg 1992). This study suggests that it could be an advantage to take steroids intermittently which would also diminish their harms.

It could be discussed whether we were too liberal by including crossover trials for which we assumed that no important carryover effects had occurred. We believe our approach is justified since one would not expect carryover problems for drugs with relatively quick and reversible symptomatic effects such as steroids or non-steroidal, anti-inflammatory drugs in patients with rheumatoid arthritis. In fact, in a meta-analysis of non-steroidal, anti-inflammatory drugs, very similar results were obtained with the two trial designs (Gøtzsche 1989b). Only three studies were of a group comparative design, and the heterogeneity we found could not be explained by type of design.

The titles of the included trials were generally quite uninformative and some of them would not have been too easy to find since they were performed within experiments designed to study other factors. Several of the studies were retrieved from an archive in possession of one of the authors, assembled during work on a thesis (Gøtzsche 1990b), before the electronic data searches were performed. The authors of a long-term study (van Gestel 1995) had only found one of five trials comparing steroids with placebo in long-term studies, and none of the nine short-term trials included in our review. These short-term trials were described in eleven reports which were all indexed in PubMed with the term for rheumatoid arthritis; in addition, all but one (Jasani 1968) contained the terms for clinical trial or comparative study. Further, all nine trials were identifiable by using the search term placebo* and (prednisone or prednisolone). This illustrates the value of a systematic and careful search of the literature before starting new clinical trials. To diminish the risk of unnecessary research, funding bodies and ethical review committees should demand a systematic review of the relevant literature before approving of new clinical research (Savulescu 1996).

We found two studies of matched cohorts that described the harms of corticosteroids (McDougall 1994; Saag 1994). One of the matched cohort studies had included 112 patients who had received 15 mg prednisolone or less for at least 12 months and 112 matched controls (Saag 1994). It used a survival type analysis and found a large difference in time to first adverse event, with a total of 92 events in the steroid group and 31 in the untreated group. The risk of fracture increased with increasing doses: odds ratio 32.3 (95% confidence interval 4.6 to 220) for >10-15 mg prednisolone daily, 4.5 (95% CI 2.1 to 9.6) for 5-10 mg, and 1.9 (95% CI 0.8 to 4.7) for less than 5 mg daily. The overall risks for first event were: fracture 3.9 (95% CI 0.8 to 18.1), infection 8.0 (95% CI 1.0 to 64.0), gastrointestinal bleed or ulcer 3.3 (95% CI 0.9 to 12.1). This study also included patients who received oral steroid "pulses", which do not necessarily lead to the same incidence and severity of adverse effects as continuous low-dose treatment. The other cohort study followed two groups of 122 patients for 10 years (McDougall 1994). Fractures were noted in 31 vs 19 patients, osteonecrosis in 5 vs 2, and cataracts in 36 vs 22.

The main problem with such studies are that the two groups can never be completely comparable, since patients treated with steroids must be expected to be more severely affected than those not treated. This fact may escape notice by traditional measures of morbidity, or the difference may be statistically significantly for one (McDougall 1994) or more (Saag 1994) indicators of disease severity, as in the two cohort studies we reviewed. It is noteworthy, for example, that the first study (Saag 1994) found a similarly increased risk for fractures as for ulcers, since five meta-analyses of around one hundred randomised trials of steroids in a variety of diseases have shown either no increase in risk, or, at most, a marginally increased risk of ulcers, which lacks clinical significance (Gøtzsche 1994). Another meta-analysis of 71 randomised trials, which looked at the risk of infectious complications, showed no increase in risk in patients given less than 10 mg prednisolone daily, and the relative risk for a mean dose less than 20 mg was only 1.3 (95% CI 1.0 to 1.6) (Stuck 1989), which is in contrast to the 8-fold increased risk in the cohort study (Saag 1994). Although the confidence intervals were wide in the cohort study, this illustrates the well-known dangers of non-randomised comparisons.

All treatments for rheumatoid arthritis, including non-steroidal, anti-inflammatory drugs and slow-acting antirheumatic drugs, may cause important harms that may occasionally be life-threatening. We therefore suggest that short-term prednisolone in low doses, i.e. not exceeding 15 mg daily, may be used intermittently in patients with rheumatoid arthritis, particularly if they have flares in their disease which cannot be controlled by other means. This suggestion is in accordance with detailed reviews of the harms of low-dose steroids (Caldwell 1991; Da Silva 2006). Since prednisolone is highly effective, short-term placebo controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary.

AUTHORS' CONCLUSIONS

Implications for practice

Prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means. The risk of harms needs to be considered, however, especially the risk of fractures and infections.

Implications for research

Since prednisolone is highly effective, short-term placebo controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary.

ACKNOWLEDGEMENTS

We are grateful for the unpublished data provided by Anke van Gestel and Roland Laan.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Berry 1974

Methods	Crossover study; one-week periods, and one-week wash-out. Randomisation not mentioned; only that the study was double-blind.
Participants	12 patients with definite or classical rheumatoid arthritis (ARA criteria).
Interventions	Prednisolone 15 mg/d, placebo.
Outcomes	Pain (visual analogue scale) Duration of morning stiffness Ritchie's index Joint size Paracetamol consumption Technetium index Indium index Patient preference
Notes	No test for carry-over and period effects. No data on side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Boardman 1967

Methods	Crossover study; one-week periods. Sequential analysis of joint size. Randomisation not mentioned; only that the study was double-blind.
Participants	13 patients with definite or classical rheumatoid arthritis (ARA criteria).

Boardman 1967 *(Continued)*

Interventions	Prednisone 7.5 mg/d, placebo.
Outcomes	Joint size Grip strength Patient preference
Notes	No test for carry-over and period effects. We included two patients, who the authors had excluded because of too little difference in joint size, in the analysis by assuming that their grip strength difference was zero. Grip strength data were missing for another patient. Two patients on prednisone had 'subjective reactions'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Böhm 1967

Methods	Four-way crossover study; eight-day periods. Randomisation method not described. Double-blind.
Participants	20 patients with rheumatoid arthritis.
Interventions	Prednisolone 2.5 mg, two combination drugs, placebo.
Outcomes	Pain (4 point ranking scale)
Notes	No test for carry-over and period effects. No data on side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dick 1970

Methods	Four-way crossover study; one-week periods. Randomisation method not described. Double-blind.
Participants	24 patients with definite or classical rheumatoid arthritis (ARA criteria).
Interventions	Prednisolone 10 mg/d, ibuprofen 1200 mg/d, aspirin 4 g/d, placebo.
Outcomes	Global evaluation Knee tenderness score Ritchie's index Grip strength Joint size

Dick 1970 *(Continued)*

Notes	No test for carry-over and period effects. Average of ibuprofen and aspirin used in the analysis. No data on side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jasani 1968

Methods	Four-way crossover study; one-week periods. Randomisation method not described. Double-blind.
Participants	9 patients with definite or classical rheumatoid arthritis (ARA criteria).
Interventions	Prednisolone 15 mg/d, ibuprofen 750 mg/d, aspirin 5 g/d, placebo.
Outcomes	Joint pain Joint stiffness Pain index (composite scale) Ritchie's index Grip strength Joint size
Notes	No test for carry-over and period effects. Average of ibuprofen and aspirin used in the analysis. No side effects occurred with prednisolone or placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kirwan 2004

Methods	Group comparative study; 12 weeks, data after 2 weeks available. Randomisation method: "Predefined sequence of randomly generated allocations kept in sealed envelopes", "Patients allocated to next available study number". Double-blind: "double-dummy".
Participants	143 patients with rheumatoid arthritis (ARA criteria).
Interventions	Budesonide 3 and 9 mg, 7.5 mg prednisolone, placebo.
Outcomes	Tender joint count Pain Global assessments Physical function (HAQ) SF-36
Notes	Data after 2 weeks from author; SDs estimated from graphs after 4 weeks.

Kirwan 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lee 1973a

Methods	Three-way crossover study; one-week periods. Randomisation method not described. Double-blind.
Participants	21 patients with definite or classical rheumatoid arthritis (ARA criteria).
Interventions	Prednisolone 15 mg/d, aspirin 5 g/d, placebo.
Outcomes	Functional index Ritchie's index Time to walk 50 feet Grip strength
Notes	No test for carry-over and period effects. No data on side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lee 1973b

Methods	Group comparative study of three drugs; two weeks. Randomisation method not described. Single-blind; probably the patient was blinded.
Participants	141 patients with rheumatoid arthritis according to ARA criteria.
Interventions	Prednisone 15 mg/d, aspirin 3.9 g/d, placebo.
Outcomes	Global evaluation Pain (5 point ranking scale) Number of days withdrawn from trial
Notes	Thirteen patients were excluded after randomisation (failed to complete the trial), three on prednisolone, five on aspirin, and five on placebo. One patient developed acute psychosis on prednisone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lee 1974

Methods	Three-way crossover study; one-week periods. Randomisation method not described. Double-blind.
Participants	18 patients with definite or classical rheumatoid arthritis (ARA criteria).
Interventions	Prednisolone 10 mg/d, sodium salicylate 4 g/d, placebo.
Outcomes	Functional index Ritchie's index Grip strength
Notes	No test for carry-over and period effects. No data on side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stenberg 1992

Methods	Crossover study; each flare treated for five days. Randomisation not described; only that the study was double-blind, half of the patients starting on each drug.
Participants	22 patients with rheumatoid arthritis (ARA criteria).
Interventions	Prednisone (average dose 3 mg/d), placebo. Prednisone was only taken during flares: 7.5 mg day 1, 5 mg next 3 days, and 2.5 mg day 5.
Outcomes	Tender joint count Swollen joint count Pain (composite score) Global assessment Morning stiffness Painful joint count Time until fatigue Medication usage
Notes	Tested for carry-over effects. Three randomised patients were excluded because of poor response to prednisone in an introductory test period. We included these patients in the analysis by assuming that the differences between prednisone and placebo were zero. One additional patient dropped out for personal reasons. No data on short-term side effects since multiple flares were treated during a three months period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Gestel 1995

Methods	Group comparative study; 44 weeks, data after one week provided by authors. Randomisation method: list of random numbers; a pharmacist coded the packages. Double-blind.
Participants	40 patients with definite or classical rheumatoid arthritis (ARA criteria); all started parenteral gold.
Interventions	Prednisone 10 mg/d, placebo.
Outcomes	Joint pain (visual analogue scale) Global evaluation Morning stiffness Ritchie's index Number of swollen joints Grip strength Functional capacity X-ray progression
Notes	Grip strength recalculated as mm Hg from kPa. Long-term study, no data on short-term side effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Badia Flores 1969	Combination drug (prednisolone 2.5 mg + oxiphenbutazone 100 mg) vs placebo.
Capell 2004	Long-term study with assessment after 1 and 2 years (7 mg prednisolone vs placebo, 167 patients).
Chamberlain 1976	Long-term study with assessment after 1, 2, and 3 years (3 and 5 mg prednisolone vs placebo, 49 patients).
Deodhar 1973	Unbalanced design (five-way crossover trial comparing prednisolone 10 mg with placebo and three NSAIDs).
Empire Rheum 1955	Long-term study with assessment after 6 and 12 months (75 mg cortisone vs aspirin 4 g, 100 patients).
Fearnley 1966	No data on dispersion (prednisone 7.5 mg vs flufenamic acid 600 mg).
Gum 1966	Only 50 of 68 patients had rheumatoid arthritis; combination drug (paramethasone 1.5 g + aspirin 3 g + propoxyphene 192 mg vs aspirin 3 g + propoxyphene 192 mg).
Hansen 1999	Dose of prednisolone too high, 30 mg daily in first week.
Hantzschel 1976	Not a randomised trial.
Harris 1983	Long-term study with assessment after 12 and 24 weeks (prednisone 5 mg vs placebo, 34 patients).

Study	Reason for exclusion
Jick 1965	Combination drug (dexamethasone 1.5 mg vs dexamethasone 0.75 mg + aspirin 1.5 g).
Joint Committee 1954	Cortisone dose too high (300-100 mg in the first week, average dose corresponding to 16 mg prednisolone, comparison with aspirin 6 g, 62 patients).
Joint Committee 1959	Prednisolone dose 20 mg initially with an average of 17.4 mg after 4 weeks. Long-term study vs aspirin or other analgesics, 84 patients.
Kirwan 1995	Long-term study with no short-term data.
Kvien 1982	Juvenile rheumatoid arthritis (prednisolone 0.4 mg/kg vs placebo).
Leszczynski 2000	Concerns osteoporosis, no clinical outcomes.
Million 1984	Randomised to activity + steroid and to rest; therefore, not valid for testing the effect of steroid versus no steroid. Further, the dose was up to 20 mg prednisolone.
Murthy 1978	No data presented on the original interval scales, only data on reduced (trinomial) scales shown.
Rau 2000	Concerns radiological progression, no clinical data.
Siegmeth 1974	Combination drug (prednisolone 2.5 mg + oxiphenbutazone 100 mg vs flufenamic acid 200 mg).
Slonim 1969	Stepwise increasing dose of methylprednisolone up to 16 mg but placebo group received 4 mg methylprednisolone daily.
van Everdingen 2002	Long-term study with assessments every 3 months (10 mg prednisolone vs placebo, 81 patients with early disease).
Webb 1973	Only joint size recorded (prednisolone 7.5 mg vs aspirin 4.8 g vs placebo).
Zuckner 1969	Describes an unpublished crossover trial of 20 patients; combination therapy, steroid + analgesics versus analgesics.

DATA AND ANALYSES

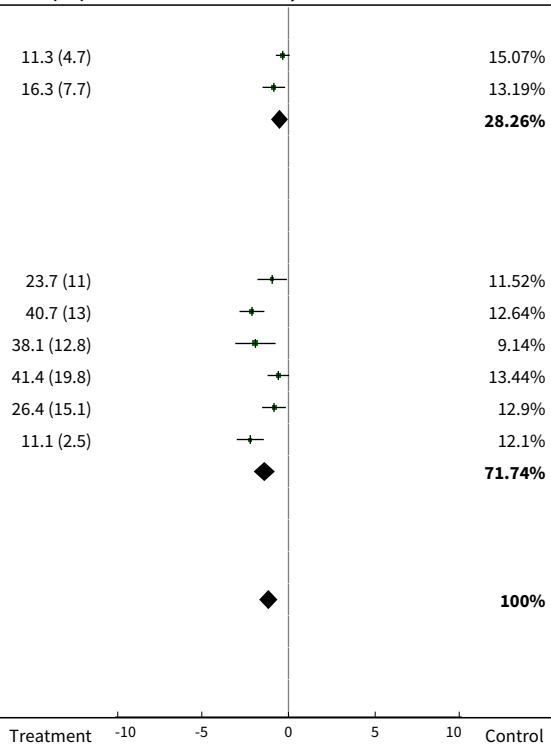
Comparison 1. Oral corticosteroids vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint tenderness	8	392	Std. Mean Difference (IV, Random, 95% CI)	-1.16 [-1.69, -0.64]
1.1 Allocation concealment	2	182	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.01, -0.03]
1.2 Allocation concealment unclear	6	210	Std. Mean Difference (IV, Random, 95% CI)	-1.40 [-2.01, -0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Pain	7	416	Std. Mean Difference (IV, Random, 95% CI)	-1.51 [-2.31, -0.71]
2.1 Allocation concealment	2	182	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.58, 0.23]
2.2 Allocation concealment unclear	5	234	Std. Mean Difference (IV, Random, 95% CI)	-1.89 [-1.00, -0.79]
3 Grip strength	6	208	Std. Mean Difference (IV, Random, 95% CI)	0.41 [0.13, 0.69]
3.1 Allocation concealment	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.40, 0.84]
3.2 Allocation concealment unclear	5	168	Std. Mean Difference (IV, Random, 95% CI)	0.46 [0.15, 0.76]

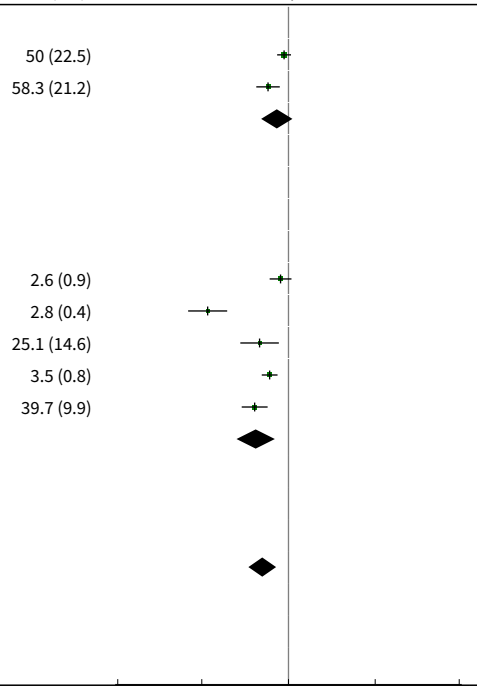
Analysis 1.1. Comparison 1 Oral corticosteroids vs placebo, Outcome 1 Joint tenderness.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.1.1 Allocation concealment							
Kirwan 2004	111	9.7 (4.7)	31	11.3 (4.7)		15.07%	-0.33[-0.73,0.07]
van Gestel 1995	20	10.8 (4.7)	20	16.3 (7.7)		13.19%	-0.85[-1.49,-0.2]
Subtotal ***	**131**		**51**			**28.26%**	**-0.52[-1.01,-0.03]**
Heterogeneity: Tau^2=0.06; Chi^2=1.75, df=1(P=0.19); I^2=42.96%							
Test for overall effect: Z=2.09(P=0.04)							
1.1.2 Allocation concealment unclear							
Berry 1974	12	13 (11)	12	23.7 (11)		11.52%	-0.94[-1.79,-0.09]
Dick 1970	24	17.6 (8)	24	40.7 (13)		12.64%	-2.11[-2.82,-1.39]
Jasani 1968	9	16.2 (8.7)	9	38.1 (12.8)		9.14%	-1.91[-3.07,-0.74]
Lee 1973a	21	30.5 (16.5)	21	41.4 (19.8)		13.44%	-0.59[-1.21,0.03]
Lee 1974	18	14.6 (12.4)	18	26.4 (15.1)		12.9%	-0.84[-1.52,-0.15]
Stenberg 1992	21	6.3 (1.7)	21	11.1 (2.5)		12.1%	-2.2[-2.98,-1.42]
Subtotal ***	**105**		**105**			**71.74%**	**-1.4[-2.01,-0.79]**
Heterogeneity: Tau^2=0.42; Chi^2=18.58, df=5(P=0); I^2=73.08%							
Test for overall effect: Z=4.48(P<0.0001)							
Total ***	**236**		**156**			**100%**	**-1.16[-1.69,-0.64]**
Heterogeneity: Tau^2=0.44; Chi^2=33.21, df=7(P<0.0001); I^2=78.92%							
Test for overall effect: Z=4.33(P<0.0001)							
Test for subgroup differences: Chi^2=12.88, df=1 (P=0), I^2=92.23%							



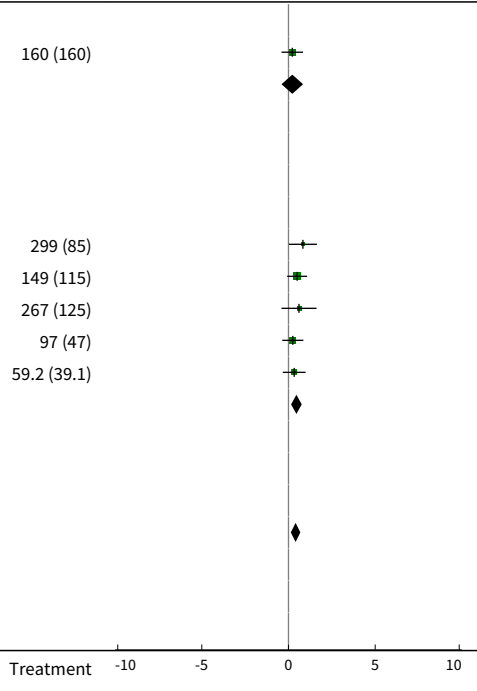
Analysis 1.2. Comparison 1 Oral corticosteroids vs placebo, Outcome 2 Pain.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.2.1 Allocation concealment							
Kirwan 2004	111	44.3 (22.4)	31	50 (22.5)		15.75%	-0.25[-0.65,0.15]
van Gestel 1995	20	35.6 (16.2)	20	58.3 (21.2)		14.66%	-1.18[-1.86,-0.5]
Subtotal ***	**131**		**51**			**30.41%**	**-0.67[-1.58,0.23]**
Heterogeneity: Tau^2=0.35; Chi^2=5.32, df=1(P=0.02); I^2=81.21%							
Test for overall effect: Z=1.46(P=0.14)							
1.2.2 Allocation concealment unclear							
Böhm 1967	20	2.2 (1)	20	2.6 (0.9)		14.88%	-0.46[-1.09,0.17]
Dick 1970	24	0.5 (0.6)	24	2.8 (0.4)		12.36%	-4.66[-5.79,-3.54]
Jasani 1968	9	5.7 (5.7)	9	25.1 (14.6)		12.45%	-1.67[-2.78,-0.56]
Lee 1973b	45	2.6 (0.8)	41	3.5 (0.8)		15.56%	-1.09[-1.54,-0.63]
Stenberg 1992	21	23.5 (5.9)	21	39.7 (9.9)		14.34%	-1.95[-2.7,-1.2]
Subtotal ***	**119**		**115**			**69.59%**	**-1.89[-3,-0.79]**
Heterogeneity: Tau^2=1.41; Chi^2=45.01, df=4(P<0.0001); I^2=91.11%							
Test for overall effect: Z=3.35(P=0)							
Total ***	**250**		**166**			**100%**	**-1.51[-2.31,-0.71]**
Heterogeneity: Tau^2=1.01; Chi^2=64.92, df=6(P<0.0001); I^2=90.76%							
Test for overall effect: Z=3.71(P=0)							
Test for subgroup differences: Chi^2=14.58, df=1 (P=0), I^2=93.14%							



Analysis 1.3. Comparison 1 Oral corticosteroids vs placebo, Outcome 3 Grip strength.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.3.1 Allocation concealment							
van Gestel 1995	20	191 (112)	20	160 (160)		19.68%	0.22[-0.4,0.84]
Subtotal ***	**20**		**20**			**19.68%**	**0.22[-0.4,0.84]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.69(P=0.49)							
1.3.2 Allocation concealment unclear							
Boardman 1967	13	372 (85)	13	299 (85)		11.68%	0.83[0.02,1.64]
Dick 1970	24	213 (136)	24	149 (115)		22.99%	0.5[-0.08,1.08]
Jasani 1968	8	356 (151)	8	267 (125)		7.47%	0.61[-0.4,1.62]
Lee 1973a	21	109 (47)	21	97 (47)		20.62%	0.25[-0.36,0.86]
Lee 1974	18	73.1 (43.5)	18	59.2 (39.1)		17.56%	0.33[-0.33,0.99]
Subtotal ***	**84**		**84**			**80.32%**	**0.46[0.15,0.76]**
Heterogeneity: Tau^2=0; Chi^2=1.52, df=4(P=0.82); I^2=0%							
Test for overall effect: Z=2.91(P=0)							
Total ***	**104**		**104**			**100%**	**0.41[0.13,0.69]**
Heterogeneity: Tau^2=0; Chi^2=1.97, df=5(P=0.85); I^2=0%							
Test for overall effect: Z=2.91(P=0)							
Test for subgroup differences: Chi^2=0.45, df=1 (P=0.5), I^2=0%							



Comparison 2. Oral corticosteroids vs NSAIDs

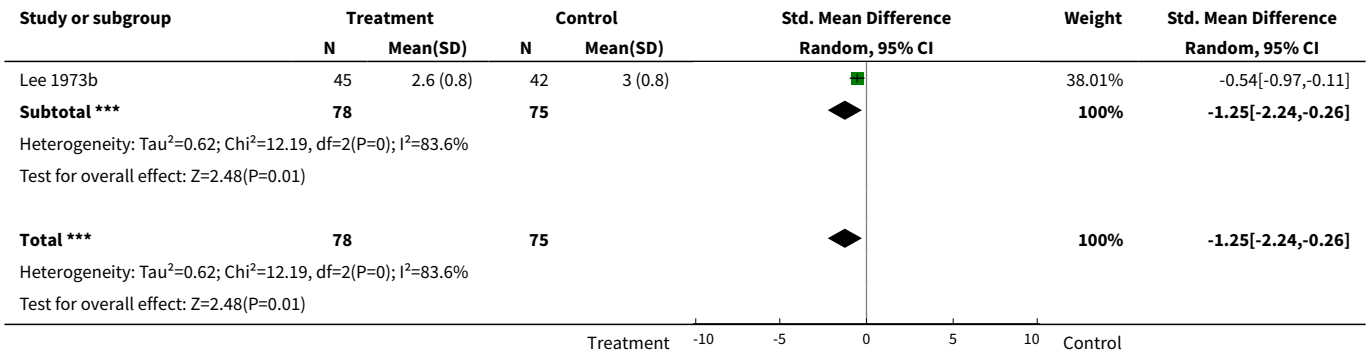
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint tenderness	4	144	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.16, -0.11]
1.1 Allocation concealment unclear	4	144	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.16, -0.11]
2 Pain	3	153	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-2.24, -0.26]
2.1 Allocation concealment unclear	3	153	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-2.24, -0.26]
3 Grip strength	4	142	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.02, 0.64]
3.1 Allocation concealment unclear	4	142	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.02, 0.64]

Analysis 2.1. Comparison 2 Oral corticosteroids vs NSAIDs, Outcome 1 Joint tenderness.

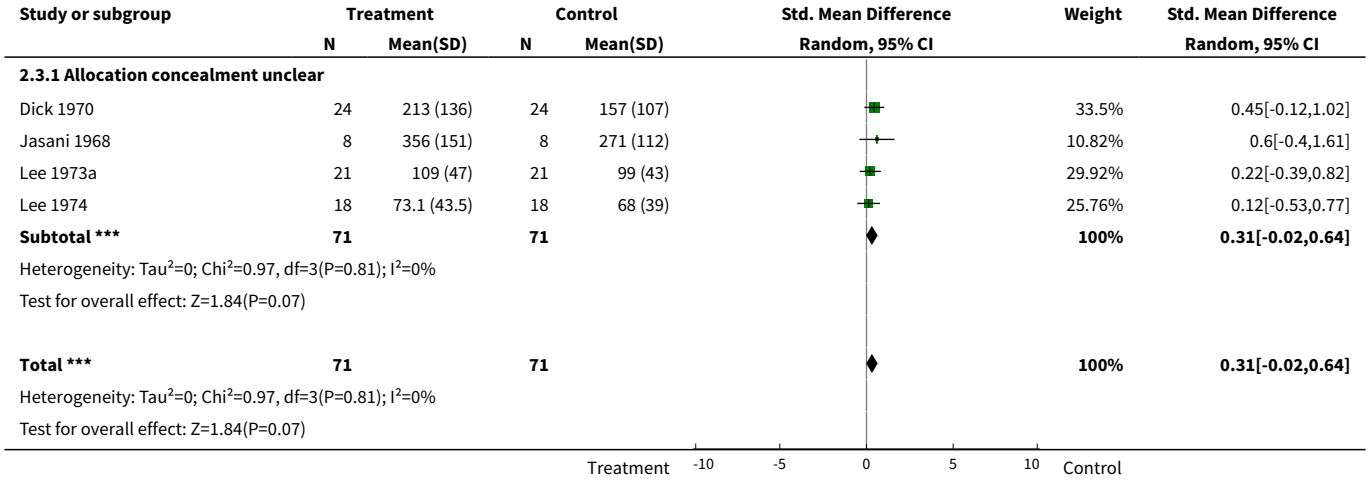
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.1.1 Allocation concealment unclear							
Dick 1970	24	17.6 (8)	24	28.7 (11.4)		28.22%	-1.11[-1.72,-0.5]
Jasani 1968	9	16.2 (8.7)	9	26.7 (8.7)		16.79%	-1.15[-2.17,-0.13]
Lee 1973a	21	30.5 (16.5)	21	37.7 (21.5)		28.25%	-0.37[-0.98,0.24]
Lee 1974	18	14.6 (12.4)	18	15.7 (13.5)		26.74%	-0.08[-0.74,0.57]
Subtotal ***	**72**		**72**			**100%**	**-0.63[-1.16,-0.11]**
Heterogeneity: Tau²=0.16; Chi²=6.73, df=3(P=0.08); I²=55.45%							
Test for overall effect: Z=2.37(P=0.02)							
Total ***	**72**		**72**			**100%**	**-0.63[-1.16,-0.11]**
Heterogeneity: Tau²=0.16; Chi²=6.73, df=3(P=0.08); I²=55.45%							
Test for overall effect: Z=2.37(P=0.02)							

Analysis 2.2. Comparison 2 Oral corticosteroids vs NSAIDs, Outcome 2 Pain.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.2.1 Allocation concealment unclear							
Dick 1970	24	0.5 (0.6)	24	1.7 (0.6)		33.97%	-1.97[-2.66,-1.27]
Jasani 1968	9	5.7 (5.7)	9	16.9 (9.7)		28.02%	-1.34[-2.39,-0.29]



Analysis 2.3. Comparison 2 Oral corticosteroids vs NSAIDs, Outcome 3 Grip strength.



ADDITIONAL TABLES

Table 1. Harms in moderate- and long-term studies

Study	Drugs	Length of study	Number of patients	Harms
Capell 2004	Prednisolone 7 mg, placebo	2 years	84 vs 83	Withdrawals: 6 (3 weight gain, facial swelling, nausea, gastrointesinal bleeding) vs 2 (nausea, diarrhoea); Fractures: none reported; No difference in bone mineral content, blood pressure or weight.
Chamberlain 1976	Prednisolone 3 and 5 mg, placebo	2 years	20 vs 10 vs 19	Withdrawals: none because of harms; Vertebral fractures: 1 vs 0 vs 1; Moon face (difficult to decide): 5 vs 2 vs 1; Mild dyspepsia: 3 vs 4 vs 4.
Empire Rheum 1955	Cortisone 75 mg, Aspirin 4 g	3 years	50 vs 50	Withdrawals: 3 (2 hypertension, indigestion) vs 5(gastrointestinal symptoms); Fractures: 1 (after a fall) vs 0; Oedema: 4 vs 0; Gastrointestinal symptoms: 4 vs 17; Mild psychiatric disturbance: 4 vs 0; Infection: 10 vs 4. (These are 1-year data)

Table 1. Harms in moderate- and long-term studies *(Continued)*

Harris 1983	Prednisone 5 mg, placebo	2 years	18 vs 16	Withdrawals: none reported; Vertebral fractures detected with X-ray: 2 vs 0; Ocular changes: none.
Joint Committee 1954	Cortisone 80 mg, Aspirin 4.5 g	1 year	30 vs 31	Withdrawals: none because of harms; Fractures: none reported; Most common harms on steroid: 11 moon face or rubicundity, 5 depression, 4 euphoria; on Aspirin: 13 gastrointestinal symptoms, 11 tinnitus, 10 deafness.
Joint Committee 1959	Prednisolone 17.4 mg, NSAIDs	2 years	45 vs 39	Withdrawals: none because of harms; Vertebral fractures detected with X-ray: 2 vs 1; Acute phychosis: 2 vs 0; Peptic ulcer: 3 vs 0; Major infection: 4 vs 3.
Kirwan 1995	Prednisolone 7.5 mg, placebo	2 years	61 vs 67	Withdrawals: 1 vs 2 hypertension and weight gain, 0 vs 1 diabetes; Fractures: none reported; Other harms: only listed, not divided on treatment groups.
Kirwan 2004	Budesonide 3 and 9 mg, prednisolone 7.5 mg, placebo	12 weeks	37, 36, 39, 31	Withdrawals: no data, only symptoms listed; Serious harms: budesonide 3 mg (1 angina), prednisolone (1 with ischaemic heart diesase died); Fractures: none reported; Respiratory infection: 7 vs 4 vs 6 vs 1; Viral infection: 4 vs 1 vs 0 vs 0. Abdominal pain: 4 vs 3 vs 4 vs 2.
Rau 2000	Prednisolone 5 mg, placebo	2 years	80 vs 86	Withdrawals: none; Vertebral fractures detected with X-ray: none; Other fractures: 1 (pubic ramus) vs 0 (plus 4 caused by trauma, not divided on treatment groups); Cushing: 5 vs 0; Hypertension: 6 vs 2; Weight gain: 5 kg vs 0.3 kg; Cataract: 5 vs 6; Gastric ulcers: 3 vs 0. Headache: 4 vs 0.
Stenberg 1992	Prednisolone 3 mg, placebo	3 months	18 (crossover)	Withdrawals: none reported; Fractures: none reported; Weight gain: 3 vs 2; Hypertension: 1 vs 3; Gastrointestinal symptoms: 2 vs 2; Insomnia: 1 vs 0.
van Everdingen 2002	Prednisolone 10 mg, placebo	2 years	40 vs 41	Withdrawals: none because of harms; Vertebral fractures detected with X-ray: 5 vs 2; Respiratory infections: 13 vs 13; Diabetes: 2 vs 1; Peptic ulcer: 1 vs 2; Depression: 1 vs 2.
van Gestel 1995	Prednisolone 10 mg (tapered to 2.5 mg), placebo	44 weeks	20 vs 20	Withdrawals: none reported; Vertebral fractures detected with X-ray: none; Other harms: none reported.

WHAT'S NEW

Date	Event	Description
9 November 2008	Amended	Converted to new review format. CMSD ID: C076-R

CONTRIBUTIONS OF AUTHORS

PCG wrote the draft protocol and manuscript. HKJ commented on the drafts. Both authors contributed to selection of studies and extraction of data. PCG is guarantor for the study

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Medical Research Council, Denmark.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*administration & dosage] [adverse effects]; Anti-Inflammatory Agents, Non-Steroidal [administration & dosage] [adverse effects]; Arthritis, Rheumatoid [*drug therapy]; Indomethacin [administration & dosage] [adverse effects]; Prednisolone [administration & dosage] [adverse effects]; Prednisone [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Humans