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Intra-articular corticosteroid for knee osteoarthritis (Review)

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[Intervention Review]

Intra-articular corticosteroid for knee osteoarthritis

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ABSTRACT

Background

Knee osteoarthritis is a leading cause of chronic pain, disability, and decreased quality of life. Despite the long-standing use of intra-articular corticosteroids, there is an ongoing debate about their benefits and safety. This is an update of a Cochrane review first published in 2005.

Objectives

To determine the benefits and harms of intra-articular corticosteroids compared with sham or no intervention in people with knee osteoarthritis in terms of pain, physical function, quality of life, and safety.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE (from inception to 3 February 2015), checked trial registers, conference proceedings, reference lists, and contacted authors.

Selection criteria

We included randomised or quasi-randomised controlled trials that compared intra-articular corticosteroids with sham injection or no treatment in people with knee osteoarthritis. We applied no language restrictions.

Data collection and analysis

We calculated standardised mean differences (SMDs) and 95% confidence intervals (CI) for pain, function, quality of life, joint space narrowing, and risk ratios (RRs) for safety outcomes. We combined trials using an inverse-variance random-effects meta-analysis.

Main results

We identified 27 trials (13 new studies) with 1767 participants in this update. We graded the quality of the evidence as 'low' for all outcomes because treatment effect estimates were inconsistent with great variation across trials, pooled estimates were imprecise and did not rule out relevant or irrelevant clinical effects, and because most trials had a high or unclear risk of bias. Intra-articular corticosteroids appeared to be more beneficial in pain reduction than control interventions (SMD -0.40, 95% CI -0.58 to -0.22), which corresponds to a difference in pain scores of 1.0 cm on a 10-cm visual analogue scale between corticosteroids and sham injection and translates into a number needed to treat for an additional beneficial outcome (NNTB) of 8 (95% CI 6 to 13). An I^2 statistic of 68% indicated considerable between-trial heterogeneity. A visual inspection of the funnel plot suggested some asymmetry (asymmetry coefficient -1.21, 95%CI -3.58 to 1.17). When

stratifying results according to length of follow-up, benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.48, 95% CI -0.70 to -0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to -0.21), small at 13 weeks (SMD -0.22, 95% CI -0.44 to 0.00), and no evidence of an effect at 26 weeks (SMD -0.07, 95% CI -0.25 to 0.11). An I^2 statistic of ≥ 63% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity≤0.001), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P=0.43). There was evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P=0.05) or at least 100 participants per group (P=0.013), in trials that used concomittant viscosupplementation (P=0.08), and in trials that used concomitant joint lavage (P≤0.001).

Corticosteroids appeared to be more effective in function improvement than control interventions (SMD -0.33, 95% CI -0.56 to -0.09), which corresponds to a difference in functions scores of -0.7 units on standardised Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability scale ranging from 0 to 10 and translates into a NNTB of 10 (95% CI 7 to 33). An I^2 statistic of 69% indicated a moderate to large degree of between-trial heterogeneity. A visual inspection of the funnel plot suggested asymmetry (asymmetry coefficient -4.07, 95% CI -8.08 to -0.05). When stratifying results according to length of follow-up, benefits were small to moderate at 1 to 2 weeks after end of treatment (SMD -0.43, 95% CI -0.72 to -0.14), small to moderate at 4 to 6 weeks (SMD -0.36, 95% CI -0.63 to -0.09), and no evidence of an effect at 13 weeks (SMD -0.13, 95% CI -0.37 to 0.10) or at 26 weeks (SMD 0.06, 95% CI -0.16 to 0.28). An I^2 statistic of ≥ 62% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity≤0.004), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P=0.52). We found evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P=0.023), in unpublished trials (P=0.023), in trials that used non-intervention controls (P=0.031), and in trials that used concomitant viscosupplementation (P=0.06).

Participants on corticosteroids were 11% less likely to experience adverse events, but confidence intervals included the null effect (RR 0.89, 95% CI 0.64 to 1.23, I^2=0%). Participants on corticosteroids were 67% less likely to withdraw because of adverse events, but confidence intervals were wide and included the null effect (RR 0.33, 95% CI 0.05 to 2.07, I^2=0%). Participants on corticosteroids were 27% less likely to experience any serious adverse event, but confidence intervals were wide and included the null effect (RR 0.63, 95% CI 0.15 to 2.67, I^2=0%).

We found no evidence of an effect of corticosteroids on quality of life compared to control (SMD -0.01, 95% CI -0.30 to 0.28, I^2=0%). There was also no evidence of an effect of corticosteroids on joint space narrowing compared to control interventions (SMD -0.02, 95% CI -0.49 to 0.46).

Authors' conclusions

Whether there are clinically important benefits of intra-articular corticosteroids after one to six weeks remains unclear in view of the overall quality of the evidence, considerable heterogeneity between trials, and evidence of small-study effects. A single trial included in this review described adequate measures to minimise biases and did not find any benefit of intra-articular corticosteroids.

In this update of the systematic review and meta-analysis, we found most of the identified trials that compared intra-articular corticosteroids with sham or non-intervention control small and hampered by low methodological quality. An analysis of multiple time points suggested that effects decrease over time, and our analysis provided no evidence that an effect remains six months after a corticosteroid injection.

PLAIN LANGUAGE SUMMARY

Joint corticosteroid injection for knee osteoarthritis

Review question

We searched the literature until 3 February 2015 for studies of the effects on pain, function, quality of life, and safety of intra-articular (injected into the joint) corticosteroids compared with sham injection or no treatment in people with knee osteoarthritis.

Background

Osteoarthritis is a disease associated with a breakdown of cartilage of the joints, such as the knee. When the joint loses cartilage, the body responds by growing bone abnormally, which can result in the bone becoming misshapen and the joint painful and unstable. This can affect physical function and the ability to use the joint.

Although osteoarthritis is generally thought to be of degenerative rather than inflammatory origin, an inflammatory component may be present at times. Intra-articular corticosteroids are potent anti-inflammatory agents injected inside the knee joint.

Study characteristics

After searching for all relevant studies to 3 February 2015, we found 27 randomised controlled trials with a total of 1767 participants, of a duration ranging from two weeks to one year.

Key results

Pain

• People who received intra-articular corticosteroids rated improvement in their pain to be about 3 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.
• People who received a placebo rated improvement in their pain to be about 2 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.

Another way of saying this is:
• 44 people out of 100 who receive intra-articular corticosteroids respond to treatment (44%).
• 31 people out of 100 who receive a placebo respond to treatment (31%).
• 13 more people respond to treatment with intra-articular corticosteroids than with placebo (difference of 13%).

Note that these numbers may considerably overestimate the true benefit due to the low quality of the evidence.

Physical function

• People who received intra-articular corticosteroids rated improvement in their physical function to be about 2 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.
• People who received a placebo rated improvement in their physical function to be about 1 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.

Another way of saying this is:

• 36 people out of 100 who received intra-articular corticosteroids respond to treatment (36%).
• 26 people out of 100 who received a placebo respond to treatment (26%).
• 10 more people respond to treatment with intra-articular corticosteroids than with placebo (difference of 10%).

Note that these numbers may considerably overestimate the true benefit due to the low quality of the evidence.

Side effects

• 13 people out of 100 who used intra-articular corticosteroids experienced side effects (13%).
• 15 people out of 100 who used a placebo experienced side effects (15%).
• 2 more people experienced side effects with placebo than with intra-articular corticosteroids (difference of 2%).

Dropouts because of side effects

• 6 people out of 1000 who used intra-articular corticosteroids dropped out because of side effects (0.6%).
• 17 people out of 1000 who used a placebo dropped out because of side effects (1.7%).
• 11 more people dropped out because of side effects with placebo than with intra-articular corticosteroids (difference of 1.1%).

Side effects resulting in hospitalisation, persistent disability, or death

• 3 people out of 1000 who used intra-articular corticosteroids experienced side effects resulting in hospitalisation, persistent disability, or death (0.3%).
• 4 people out of 1000 who used a placebo experienced side effects resulting in hospitalisation, persistent disability, or death(0.4%).
• 1 more person experienced side effects resulting in hospitalisation, persistent disability, or death with placebo than with intra-articular corticosteroids (difference of 0.1%).

Based on the evidence, intra-articular corticosteroids may cause a moderate improvement in pain and a small improvement in physical function, but the quality of the evidence is low and results are inconclusive. Intra-articular corticosteroids appear to cause as many side effects as a placebo. However, we do not have precise and reliable information about side effects.

Quality of evidence

We graded the quality of the evidence as low for all of our findings, which means that we have little confidence in these results. This was because results were generally highly discordant across studies and mainly based on small studies of low quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Intra-articular corticosteroid compared with sham injection for osteoarthritis of the knee

Patient or population: participants with osteoarthritis of the knee

Settings: various orthopaedic or rheumatology clinics

Intervention: intra-articular corticosteroid

Comparison: sham injection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham injection	Intra-articular corticosteroid				
Pain intensity Various pain scales. (median follow-up: 12 weeks)	**-1.8 cm change on 10-cm VAS[1]** 29% improvement	**-2.8 cm change** (Δ -1.0 cm, -1.5 to -0.6)[2] **46% improvement** (Δ 17%, 10% to 25%)[3]	SMD -0.40 (-0.58 to -0.22) Predictive interval (-1.20 to 0.40)	1749 (26)	⊕⊕⊖⊖ **low[9]**	NNTB 8 (95% CI 6 to 13)[4]
Function Various function scales. (median follow-up: 12 weeks)	**-1.2 units on WOMAC (range 0 to 10)[1]** 21% improvement	**-1.9 units on WOMAC** (Δ -0.7, -1.2 to -0.2)[5] **34% improvement** (Δ 13%, 4% to 22%)[6]	SMD -0.33 (-0.56 to -0.09) Predictive interval (-1.19 to 0.54)	1014 (15)	⊕⊕⊖⊖ **low[9]**	NNTB 10 (95% CI 7 to 33)[7]
Number of participants experiencing any adverse event (median follow-up: 17 weeks)	150 per 1000 participant-years[8]	134 per 1000 participant-years (96 to 185)	RR 0.89 (0.64 to 1.23)	84 (2)	⊕⊕⊖⊖ **low[10]**	Little evidence of harmful effect (NNTB not statistically significant)
Number of participants who withdraw because of adverse events (median follow-up: 25 weeks)	17 per 1000 participant-years[8]	6 per 1000 participant-years (1 to 35)	RR 0.33 (0.05 to 2.07)	204 (2)	⊕⊕⊖⊖ **low[10]**	Little evidence of harmful effect (NNTB not statistically significant)

Number of participants experiencing any serious adverse event (median follow-up: 26 weeks)	4 per 1000 participant-years[8]	3 per 1000 participant-years (1 to 11)	RR 0.63 (0.15 to 2.67)	331 (5)	⊕⊕⊖⊖ **low[10]**	Little evidence of harmful effect (NNTB not statistically significant)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; RR: risk ratio; SMD: standardised mean difference; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Median reduction as observed across placebo groups in large osteoarthritis trials (see methods section, Nüesch 2009).
[2] SMDs were back-transformed onto a 10-cm visual analogue scale (VAS) on the basis of a typical pooled standard deviation (SD) of 2.5 cm in large trials that assessed pain using a VAS and expressed as change based on an assumed standardised reduction of 0.72 SD units in the control group.
[3] Percentage of improvement was calculated based on median observed pain at baseline across control groups of large osteoarthritis trials of 6.1 cm on 10-cm VAS (Nüesch 2009).
[4] Absolute response risks for pain in the control groups were assumed 31% (see methods section).

[5] SMDs were back-transformed onto a standardised Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability score ranging from 0 to 10 on the basis of a typical pooled SD of 2.1 in trials that assessed function using WOMAC disability scores and expressed as change based on an assumed standardised reduction of 0.58 SD units in the control group.
[6] Percentage of improvement was calculated based on median observed WOMAC function scores at baseline across control groups of large osteoarthritis trials of 5.6 units (Nüesch 2009).
[7] Absolute response risks for function in the control groups were assumed 26% (see methods section).
[8] Median control risk across placebo groups in large osteoarthritis trials (see methods section, Nüesch 2009).

[9] Downgraded (2 levels) because: Most studies that reported this outcome are of high or unclear risk of bias, and statistical heterogeneity is large.

[10] Downgraded (3 levels) because: 50% or more of the studies that reported this outcome are of high or unclear risk of bias, and the confidence interval of the pooled estimate is wide and includes the null effect.

BACKGROUND

Description of the condition

Knee osteoarthritis is a leading cause of chronic disability in the United States (Felson 2000; Felson 2000a). It results from a multitude of both local and systemic factors. Progression of the disease leads to cartilage degeneration and thinning of the joint surface with subsequent joint pain and stiffness (Brandt 1996).

Description of the intervention

Intra-articular corticosteroid therapy has been used in knee osteoarthritis for over 50 years. The first clinical trial of intra-articular corticosteroids in knee osteoarthritis was performed in 1958 by Miller and colleagues (Miller 1958). Corticosteroids are available in both crystalline and non-crystalline forms. The crystalline triamcinolone and the non-crystalline prednisolone and methylprednisolone are used most frequently. Although this review is restricted to osteoarthritis of the knee joint, intra-articular corticosteroids have also been evaluated in osteoarthritis of various other joints (McColl 2000; Rozental 2000).

How the intervention might work

Although osteoarthritis is generally thought to be of degenerative rather than inflammatory origin, there is evidence that an inflammatory component may be present in at least some phases of the disease (Creamer 1997). Corticosteroids are known as potent anti-inflammatory agents that act through a variety of mechanisms on different cellular levels.

Why it is important to do this review

The 2012 American College of Rheumatology (ACR) guidelines recommend the participation in exercise programs as well as weight loss (for overweight patients) as first-line treatments for symptomatic knee osteoarthritis. There is no strong recommendation for any pharmacological treatment other than over-the-counter paracetamol or nonsteroidal anti-inflammatory drugs. However, for people unresponsive to the basic treatment, there is a conditional, weak recommendation for the use of intra-articular corticosteroids (Hochberg 2012). Despite the long-standing use of intra-articular corticosteroids, there is an ongoing debate about their effectiveness and safety. Concerns have been expressed that intra-articular corticosteroids might mask the pain, enabling patients to prematurely mobilise and hereby promoting further destruction of the joint (Brandt 2001)

OBJECTIVES

To determine the benefits and harms of intra-articular corticosteroids compared with sham or no intervention in people with knee osteoarthritis in terms of pain, physical function, quality of life, and safety.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials with a control group receiving sham or no intervention.

Types of participants

At least 75% of participants with clinically or radiologically confirmed osteoarthritis of the knee. We did not consider trials that included exclusively people with inflammatory arthritis, such as rheumatoid arthritis.

Types of interventions

The experimental intervention of interest is any type of intra-articular corticosteroid. The control interventions of interest are sham intra-articular corticosteroid and no intervention.

Types of outcome measures

Primary outcomes

The main outcomes were pain and function, as currently recommended for osteoarthritis trials (Altman 1996; Pham 2004), reported within four and six weeks after end of treatment. If data on more than one pain scale were provided for a trial, we referred to a previously described hierarchy of pain-related outcomes (Jüni 2006; Reichenbach 2007), and extracted data on the pain scale that was highest on this list:

1. global pain;
2. pain on walking;
3. Western Ontario and McMaster Universities Arthritis Index (WOMAC) osteoarthritis index pain subscore;
4. composite pain scores other than WOMAC;
5. pain on activities other than walking;
6. rest pain or pain during the night;
7. WOMAC global algofunctional score;
8. Lequesne osteoarthritis index global score;
9. other algofunctional scale;
10. participant's global assessment;
11. physician's global assessment.

If data on more than one function scale were provided for a trial, we extracted data according to the hierarchy:

1. global disability score;
2. walking disability;
3. WOMAC disability subscore;
4. composite disability scores other than WOMAC;
5. disability other than walking;
6. WOMAC global scale;
7. Lequesne osteoarthritis index global score;
8. other algofunctional scale;
9. participant's global assessment;
10. physician's global assessment

Secondary outcomes

Secondary outcomes were pain and function assessed at 1 to 2, 4 to 6, 13, and 26 weeks after end of treatment, quality of life assessed at 1 to 2, 4 to 6, 13, and 26 weeks, and the following safety outcomes: joint space narrowing assessed at 1 to 2, 4 to 6, 13, and 26 weeks; the number of participants who experienced any adverse event; withdrew because of adverse events; and experienced any serious adverse events. We defined serious adverse events as events resulting in hospitalisation, prolongation of hospitalisation,

persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events, or death.

Search methods for identification of studies

Electronic searches

Please see Bellamy 2006 for information on electronic searches applied in the previous version of this review. Here, we developed a new search strategy using the electronic databases the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2015; mrw.interscience.wiley.com/cochrane/), MEDLINE, and EMBASE (Ovid SP platform). We did a top-up search in PubMed to capture citations not yet indexed in MEDLINE. We used a combination of text words and controlled terms (MeSH or MeSH-like terms), including truncated variations of preparation names and brand names combined with terms related to osteoarthritis. We applied a validated methodological filter for controlled clinical trials (Dickersin 1994; Lefebvre 2008). We have displayed the specific search algorithms in Appendix 1 and Appendix 2. We performed the searches from inception to 3 February 2015.

Searching other resources

We manually searched the proceedings of the European League Against Rheumatism at http://www.abstracts2view.com/eular/sessionindex.php, the American College of Rheumatology at http://acrannualmeeting.org/abstracts/abstract-archives/ (we no longer have access to Osteoarthritis Research Society International); used Science Citation Index to retrieve reports citing relevant articles; contacted content experts and trialists; and screened reference lists of all obtained articles. We also retrieved and screened systematic reviews published since January 2004 that evaluated the effects and safety of corticosteroid injections for knee osteoarthritis (Abdulla 2013; Arroll 2004; Avouac 2010; Bannuru 2015; Bellamy 2006; Bjordal 2007; Cheng 2012; Garg 2014; Godwin 2004; Hepper 2009; Hirsch 2013; Maricar 2013). Finally, we searched the following clinical trial registries: ClinicalTrials.gov, metaRegister of Controlled Trials (http://www.controlled-trials.com/), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/TrialSearch.aspx), and UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/)) to identify ongoing trials. We performed the last update of the search on 26 March 2015.

Data collection and analysis

We used a generic protocol with instructions for data extraction, quality assessment, and statistical analyses, which we also used in our previous Cochrane reviews (da Costa 2012; da Costa 2014; Reichenbach 2010; Rutjes 2009; Rutjes 2009a; Rutjes 2010).

Selection of studies

Please see Bellamy 2006 for information on the selection of studies in the original review. In this review update, two out of three review authors independently evaluated all titles and abstracts for eligibility (MGS, MdN and AR). We resolved disagreements by discussion. We applied no language restrictions. If multiple reports described the same trial, we considered all.

Data extraction and management

Please see Bellamy 2006 for information on data extraction and management in the original review. In this review update, two out of three review authors (BDC, RF, RH) extracted trial information independently and in duplicate using a standardised, piloted extraction form accompanied by a codebook. We resolved disagreements by discussion. We extracted characteristics of the experimental intervention (ultrasound-guided injection, use of local anesthetic, crystalline preparation, and prednisolone equivalance), the type of control used, dosage, frequency, duration of treatment, participant characteristics, types of measures used and pain-, function-, and quality of life-related outcomes, trial design, trial size, duration of follow-up, type and source of financial support, and publication status. When necessary, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data from the first period only. Whenever possible, we used results from an intention-to-treat analysis.

Assessment of risk of bias in included studies

Two out of three review authors (BDC, RF, RH) assessed randomisation, blinding, and adequacy of analyses independently and in duplicate (Jüni 2001). We resolved disagreements by consensus. We assessed two components of randomisation: generation of allocation sequences and concealment of allocation. We considered generation of sequences to be adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate included random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards, and drawing lots. We considered trials using an unpredictable allocation sequence to be randomised and trials using potentially predictable allocation mechanisms, such as alternation or the allocation of participants according to date of birth to be quasi-randomised. We considered concealment of allocation to be adequate if participants and investigators responsible for participant selection were unable to suspect before allocation which treatment was next. Methods considered adequate included central randomisation; pharmacy-controlled randomisation using identical, pre-numbered containers; and sequentially numbered, sealed, opaque envelopes. We considered blinding of participants to be adequate if a sham injection was used with a syringe that was identical in appearance to the control intervention, or an attempt was made to hide the participant's view of the injected knee by placing screens, for example. We considered blinding of therapists to be adequate if a credible blinding attempt was described, such as the use of independently prepared, opaque syringes. We considered analyses to be performed according to the intention-to-treat principle if all randomised participants were included in the analysis. We further assessed the reporting of primary outcomes, sample size calculations, and funding source. Finally, we used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2011), defined as the extent of confidence into the estimates of treatment benefits and harms.

Measures of treatment effect

We summarised continuous outcomes using standardised mean differences (SMD) with 95% confidence intervals (CI), with the differences in mean change from baseline values across treatment groups divided by the pooled standard deviation (SD). If differences in mean change were unavailable, we used differences in mean values at the end of the treatment (da Costa 2013). If some of the required data were unavailable, we used approximations, as previously described (Reichenbach 2007). An SMD of -0.20 SD units can be considered a small difference between the experimental and control groups, an SMD of -0.50 a moderate difference, and

-0.80 a large difference (Cohen 1988; Jüni 2006). SMDs can also be interpreted in terms of the percent of overlap of the experimental group's scores with scores of the control group. An SMD of -0.20 indicates an overlap in the distribution of pain or function scores in about 85% of cases, an SMD of -0.50 in about 67%, and an SMD of -0.80 in about 53% of cases (Cohen 1988; Jüni 2006). On the basis of a median pooled SD of 2.5 cm, found in large-scale osteoarthritis trials that assessed pain using a 10-cm visual analogue scale (VAS) (Nüesch 2009), SMDs of -0.20 correspond to approximate differences in pain scores between experimental and control groups of 0.5 cm on a 10-cm VAS, -0.50 of 1.25 cm, and -0.80 of 2 cm. We back transformed SMDs for function to a standardised WOMAC disability score (Bellamy 1995), ranging from 0 to 10 on the basis of a median pooled SD of 2.1 units observed in large-scale osteoarthritis trials (Nüesch 2009). We expressed binary outcomes as risk ratios (RR) with 95% CI.

Data synthesis

We used a standard inverse-variance random-effects meta-analysis to combine the trials (DerSimonian 1986). We quantified heterogeneity between trials using the I^2 statistic (Higgins 2003), which describes the percentage of variation across trials that is attributable to heterogeneity rather than to chance. I^2 values of 25% may be interpreted as low, 50% as moderate, and 75% as high between-trial heterogeneity (da Costa 2014a), although interpretation of I^2 depends on the size and number of trials included (Rucker 2008). Each trial contributed once to our main effectiveness analyses with the effect estimate closer to our primary time point of interest at four to six weeks. We investigated the association between trial size and treatment effects in contour-enhanced funnel plots (Peters 2008), plotting effect sizes on the vertical axis against their standard errors on the horizontal axis (Sterne 2001; Sterne 2011; Thompson 1999), accompanied by a regression test for asymmetry (Egger 1997). We then performed stratified analyses of the primary outcomes, pain and function, accompanied by interaction tests according to the following trial characteristics: concealment of allocation (adequate versus inadequate or unclear), blinding of participants (adequate versus inadequate or unclear), blinding of therapists (adequate versus inadequate or unclear), type of control (placebo versus no intervention), analysis in accordance with the intention-to-treat principle (yes versus no or unclear), trial size, funding (funding independent of industry versus industry or unclear source of funding), publication type (full journal article versus other type or unpublished material), ultrasound-guidance of injections (yes versus no or unclear), use of local anaesthetic (yes versus no or unclear), use of crystalline preparation (yes versus no or unclear), prednisolone equivalence dose (≥ 50 mg versus < 50 mg), use of intra-articular viscosupplementation as co-intervention (yes versus no or unclear), and use of joint lavage as co-intervention (yes versus no or unclear). We prespecified a cutoff of 100 allocated participants per trial arm to distinguish between small and large trials. A sample size of 2 x 100 participants will yield more than 80% power to detect a small to moderate SMD of -0.40 at a two-sided P value of 0.05, which corresponds to a difference of 1 cm on a 10-cm VAS between the experimental and control intervention (Nüesch 2010). Since only one large trial was available, we also used a less stringent cutoff of 50 participants per arm as previously described (Nüesch 2013). Two arms with 50 participants each will yield more than 80% power to detect a moderate to large SMD of -0.60. We calculated prednisolone equivalence doses, with prednisolone 10 mg considered equivalent to betametasone 1.6 mg, cortivazol 0.8 mg, dexamethasone 1.6 mg, hydrocortisone 40 mg, methylprednisolone 8 mg, and triamcinolone 8 mg. Interaction tests were based on z scores of the difference in effect sizes between strata divided by the corresponding standard error.

We converted SMDs of pain intensity and function to number needed to treat for an additional beneficial outcome on pain or function as compared with placebo (NNTB), and number needed to treat for an additional harmful outcome (NNTH) (da Costa 2012a). We defined treatment response as a 50% improvement in scores (Clegg 2006; Dworkin 2008; Dworkin 2009). With a median standardised pain intensity at baseline of 2.4 SD units, observed in large osteoarthritis trials (Nüesch 2009), this corresponds to a mean decrease in scores of 1.2 SD units. Based on the median standardised decrease in pain scores of 0.72 SD units (Nüesch 2009), we calculated that a median of 31% of participants in the placebo group would achieve an improvement of pain scores of 50% or more. We used this percentage as the control group response rate to calculate NNTBs for pain. Based on the median standardised WOMAC function score at baseline of 2.7 SD units and the median standardised decrease in function scores of 0.58 SD units (Nüesch 2009), 26% of participants in the placebo group would achieve a reduction in function of 50% or more. Again, we used this percentage as the control group response rate to calculate NNTBs for function. We used the median risks of 150 patients with adverse events per 1000 patient-years, four patients with serious adverse events per 1000 patient-years, and 17 dropouts due to adverse events per 1000 patient-years as observed in placebo groups in large osteoarthritis trials to calculate NNTHs for safety outcomes (Nüesch 2009). All P values were two-sided. We performed analyses using Review Manager 5.3 (RevMan 2014), and STATA version 14.0 (StataCorp, College Station, Texas).

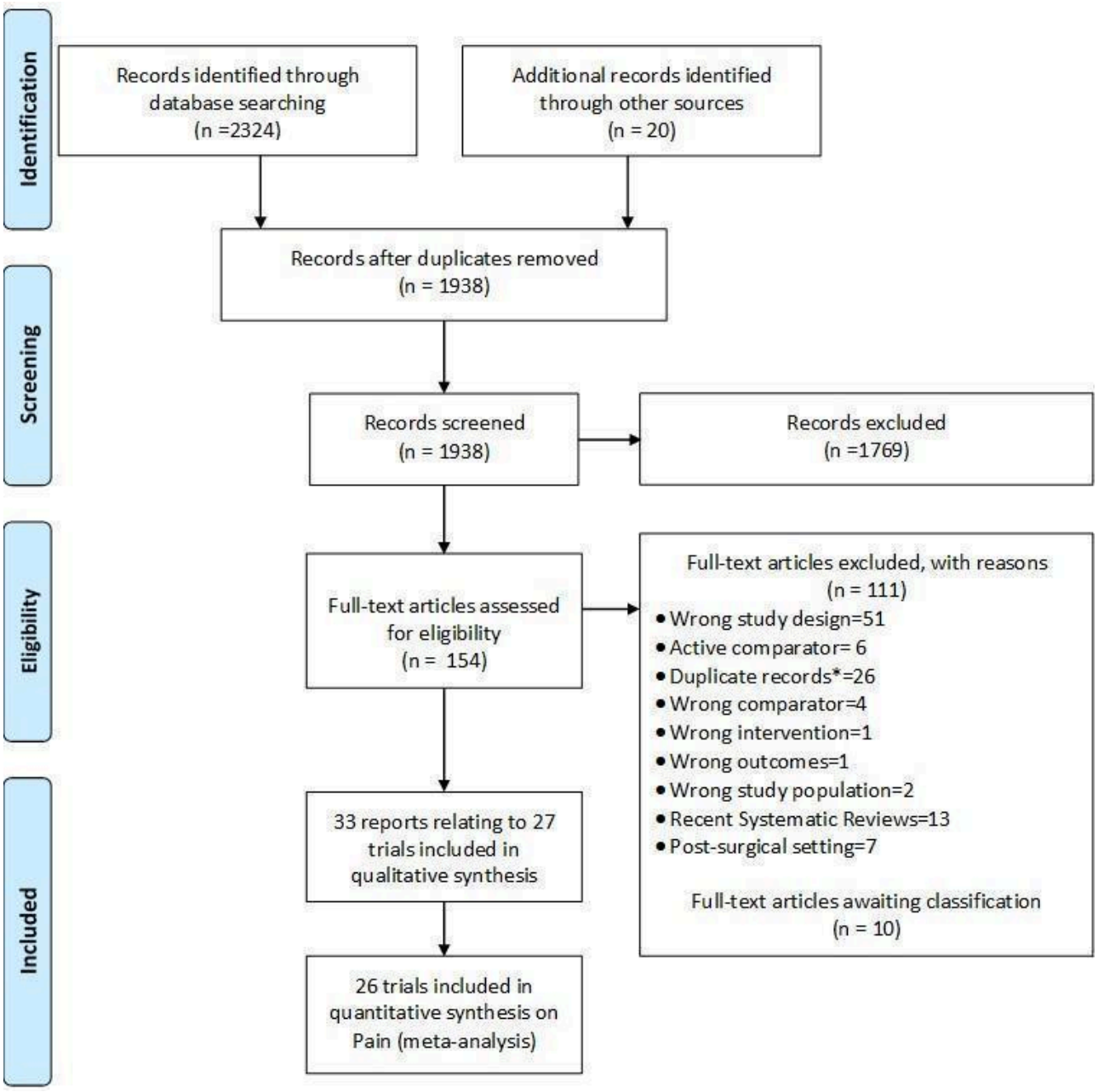
RESULTS

Description of studies

Results of the search

We identified 2324 potentially relevant references through our electronic searches and 20 additional references through other sources (Figure 1). We excluded 1769 references after screening titles and abstracts and retrieved 154 potentially relevant references for full-text assessment. We included 33 reports on 27 RCTs in the review.

Figure 1. Study flow chart. *records with the exact same bibliographic information of another already-screened record.



Included studies

Twenty-six trials reported effectiveness data. We included all 26 trials in the analysis of pain outcomes, 15 trials in the analysis of function outcomes (Beyaz 2012; Campos 2013; Castro 2007; Chao 2010; Di Sante 2012; Gaffney 1995; Henriksen 2015; Lyons 2005; Petrella 2015; Popov 1989; Ravaud 1999; Raynauld 2003; Smith 2003; Yavuz 2012; Young 2001), and two trials in the analysis of quality-of-life outcomes (Gaffney 1995; Henriksen 2015). Of the 26 included trials, 19 compared corticosteroid injection to sham injection (Beyaz 2012; Cederlof 1966; Chao 2010; Dieppe 1980; Friedman 1980; Gaffney 1995; Henriksen 2015; Jones 1996; NCT00414427; Lyons 2005; Miller 1958; Popov 1989; Ravaud 1999; Raynauld 2003; Schue 2011; Smith 2003; Yavuz 2012; Young 2001; Zhilyayev 2012), and 7 compared corticosteroid injection to no treatment (Campos 2013; Castro 2007; Di Sante 2012; Frías 2004; Grecomoro 1992; Ozturk 2006; Petrella 2015).

Triamcinolone was used in 15 trials (Beyaz 2012; Campos 2013; Castro 2007; Chao 2010; Dieppe 1980; Frías 2004; Friedman 1980; Gaffney 1995; NCT00414427; Ozturk 2006; Petrella 2015; Popov 1989; Raynauld 2003; Yavuz 2012; Zhilyayev 2012), methylprednisolone in seven trials (Di Sante 2012; Henriksen 2015; Lyons 2005; Schue 2011; Smith 2003; Yavuz 2012; Young 2001), hydrocortisone in two trials (Miller 1958; Popov 1989), prednisolone in two trials (Cederlof 1966; Jones 1996), dexamethasonephosphate in one trial (Grecomoro 1992),

betametazone disodium phosphate in one trial (Yavuz 2012), and cortivazol in one trial (Ravaud 1999). Four trials used viscosupplementation as a concomitant treatment (Campos 2013; Grecomoro 1992; Ozturk 2006; Petrella 2015), and four trials used lavage as a concomitant treatment (Castro 2007; Frías 2004; Ravaud 1999; Smith 2003). Two trials used ultrasound to assure intra-articular delivery of corticosteroid preparation (Di Sante 2012; Henriksen 2015). The median prednisolone equivalence dose across all trials was 50 mg, and the median number of corticosteroid injections was one. Trials randomised a median of 76 participants (range 16 to 205 participants).

One additional trial investigating hydrocortisone only reported safety data, on number of participants experiencing any adverse event (Wright 1960).

Excluded studies

The Characteristics of excluded studies table displays the reasons for excluding trials in this systematic review. Typical reasons were wrong study design, use of active control interventions, more than 25% of participants with rheumatoid arthritis in the sample, or the use of cross-over designs without providing sufficient information on the first phase.

Risk of bias in included studies

Figure 2 summarises the methodological characteristics and sources of funding of included trials. Two trials (7%) reported both adequate sequence generation and adequate allocation concealment (Henriksen 2015; Smith 2003), and six trials reported only adequate sequence generation (Campos 2013; Cederlof 1966; Di Sante 2012; Ozturk 2006; Petrella 2015; Raynauld 2003). In the remaining 18 trials, low quality of reporting hampered any judgement regarding sequence generation and concealment of allocation. Six trials reported the use of indistinguishable interventions to blind participants, and three trials reported the use of indistinguishable interventions to blind therapists. Nine and five trials conducted analysis of pain and function outcomes according to the intention-to-treat principle, respectively. Eleven trials received financial support from a nonprofit organisation, and no trial was explicitly supported by a commercial organisation. Twenty-three trials used parallel-group randomisation, and two were cross-over trials (Dieppe 1980; Jones 1996).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

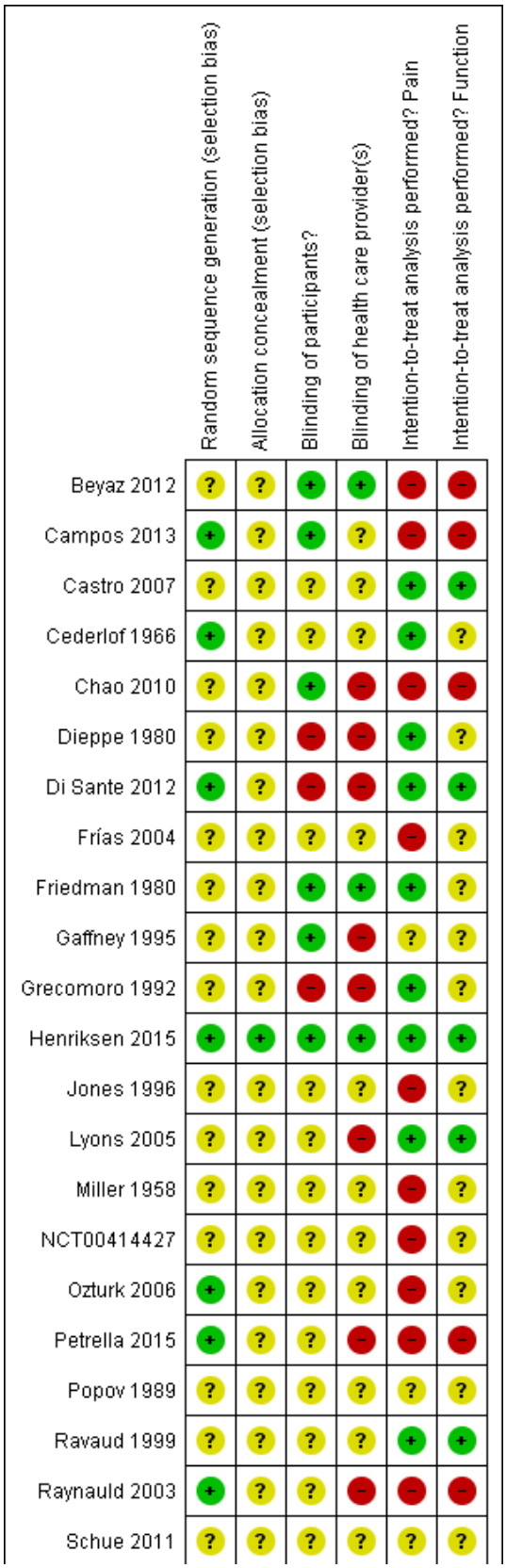
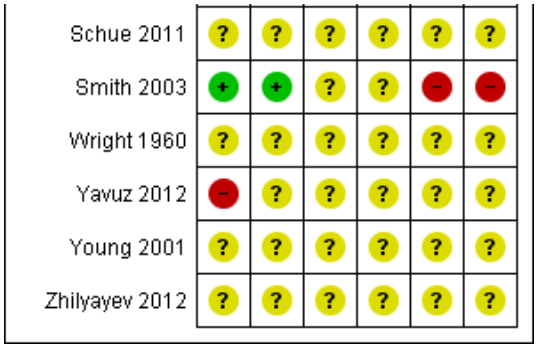


Figure 2. (Continued)



For the effectiveness outcomes pain and function, we classified the quality of the evidence as low in view of the high risk of bias in the included trials and the high heterogeneity between trials (Summary of findings for the main comparison) (Guyatt 2008).

For adverse event, dropouts due to adverse events, and serious adverse event outcomes, we classified the quality of the evidence as low because of the small number of trials reporting the outcomes and the small number of overall events, which resulted in imprecise estimates, and because we considered 50% or more of these trials to be at high risk of bias (Summary of findings for the main comparison) (Guyatt 2008).

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Knee pain

Figure 3 presents results of the overall analysis of knee pain reported closest to four to six weeks after end of treatment. Corticosteroids were more effective in pain reduction than control interventions (SMD -0.40, 95% CI -0.58 to -0.22), which corresponds to a difference in pain scores of 1.0 cm on a 10-cm VAS between corticosteroids and sham injection. This corresponds to a difference in improvement of 17% (95% CI 10% to 25%) between corticosteroids and sham injection (Summary of findings for the main comparison), which translates into a NNTB to cause one additional treatment response on pain of 8 (95% CI 6 to 13) (Summary of findings for the main comparison). An I^2 statistic of 68% indicated a moderate to large degree of between-trial heterogeneity (P for heterogeneity < 0.001). A visual inspection of the funnel plot suggested some asymmetry (asymmetry coefficient -1.21, 95% CI -3.58 to 1.17), but the corresponding regression test for asymmetry indicated no evidence for asymmetry (P = 0.30) (Figure 4).

Figure 3. Forest plot of comparison: 1 Pain, outcome: 1.1 Pain - Main.

Study or Subgroup	Std. Mean Difference	SE	IA Corticosteroid Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beyaz 2012	-0.68667	0.291396	25	25	3.8%	-0.69 [-1.26, -0.12]
Campos 2013	-0.4102612	0.1991779	52	51	4.8%	-0.41 [-0.80, -0.02]
Castro 2007	0.153865	0.25452	32	30	4.2%	0.15 [-0.34, 0.65]
Cederlof 1966	0.343675	0.443639	26	25	2.6%	0.34 [-0.53, 1.21]
Chao 2010	-0.8324666	0.2550403	34	33	4.2%	-0.83 [-1.33, -0.33]
Di Sante 2012	-1.269434	0.3481429	20	20	3.3%	-1.27 [-1.95, -0.59]
Dieppe 1980	-0.8378893	0.4273436	12	12	2.7%	-0.84 [-1.68, -0.00]
Friedman 1980	-0.06448	0.343092	17	17	3.3%	-0.06 [-0.74, 0.61]
Frías 2004	0	0.1396861	103	103	5.4%	0.00 [-0.27, 0.27]
Gaffney 1995	-0.0516039	0.2182551	42	42	4.6%	-0.05 [-0.48, 0.38]
Grecomoro 1992	0.2	0.3170589	20	20	3.6%	0.20 [-0.42, 0.82]
Henriksen 2015	-0.0392837	0.2000197	50	50	4.8%	-0.04 [-0.43, 0.35]
Jones 1996	-0.9257629	0.2721303	30	30	4.0%	-0.93 [-1.46, -0.39]
Lyons 2005	-0.566251	0.4570631	10	10	2.5%	-0.57 [-1.46, 0.33]
Miller 1958	-0.2151739	0.3313255	37	36	3.4%	-0.22 [-0.86, 0.43]
NCT00414427	-0.8803853	0.2562751	33	34	4.2%	-0.88 [-1.38, -0.38]
Ozturk 2006	-0.1368758	0.2921525	23	24	3.8%	-0.14 [-0.71, 0.44]
Petrella 2015	-0.0355	0.2463161	34	32	4.3%	-0.04 [-0.52, 0.45]
Popov 1989	-1.088324	0.4184004	19	11	2.7%	-1.09 [-1.91, -0.27]
Ravaud 1999	-0.4619007	0.2061198	49	49	4.7%	-0.46 [-0.87, -0.06]
Raynauld 2003	0.1177483	0.2464029	33	33	4.3%	0.12 [-0.37, 0.60]
Schue 2011	-0.207736	0.6144019	5	5	1.7%	-0.21 [-1.41, 1.00]
Smith 2003	-0.3261666	0.2395615	38	33	4.4%	-0.33 [-0.80, 0.14]
Yavuz 2012	-1.53523	0.234898	90	30	4.4%	-1.54 [-2.00, -1.07]
Young 2001	-0.3845994	0.3154607	21	20	3.6%	-0.38 [-1.00, 0.23]
Zhilyayev 2012	-0.4685471	0.1873348	67	52	4.9%	-0.47 [-0.84, -0.10]
Total (95% CI)			922	827	100.0%	-0.40 [-0.58, -0.22]

Heterogeneity: Tau² = 0.14; Chi² = 78.14, df = 25 (P < 0.00001); I² = 68%
Test for overall effect: Z = 4.29 (P < 0.0001)

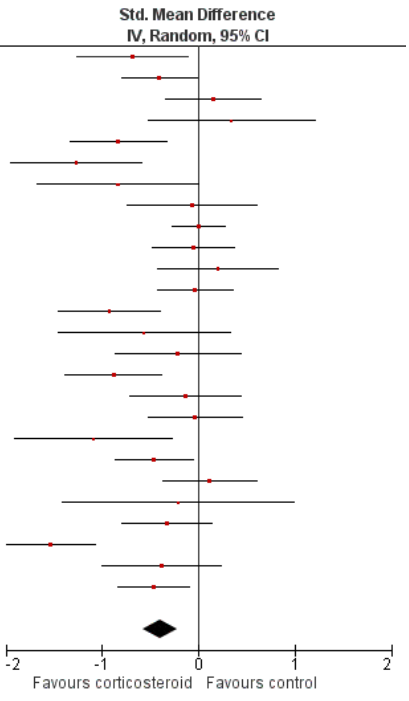


Figure 4. Contour-enhanced funnel plot for effects on knee pain. Numbers on x axis refer to standardised mean differences (SMDs), on y axis to standard errors of SMDs

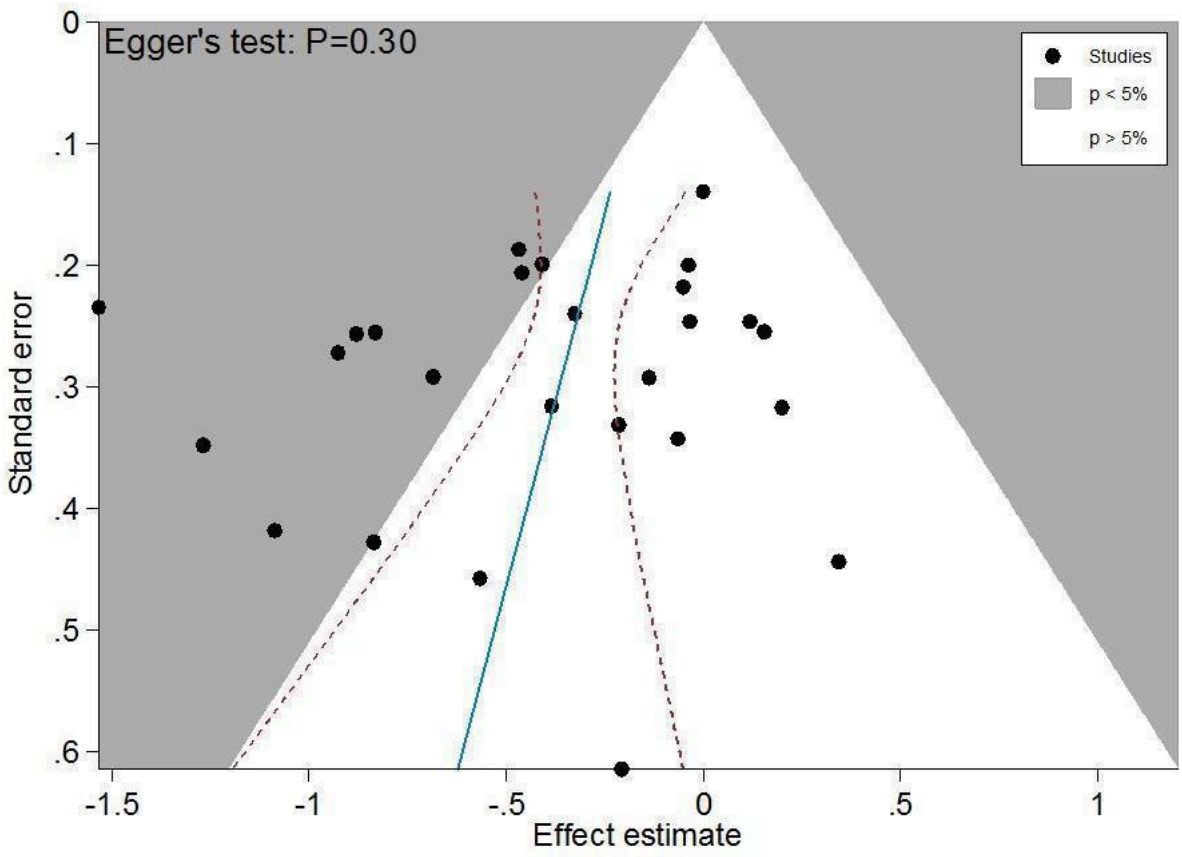


Figure 5 presents results stratified according to length of follow-up. Benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.48, 95% CI -0.70 to -0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to -0.21), small at 13 weeks (SMD -0.22, 95% CI -0.44 to 0.00), and no effect at 26 weeks (SMD -0.07, 95% CI -0.25 to 0.11). An I^2 statistic of ≥ 63% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity ≤ 0.001), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P = 0.43).

Figure 5. Forest plot of comparison: 1 Pain, outcome: 1.2 Pain - Time points. P for trend = 0.001

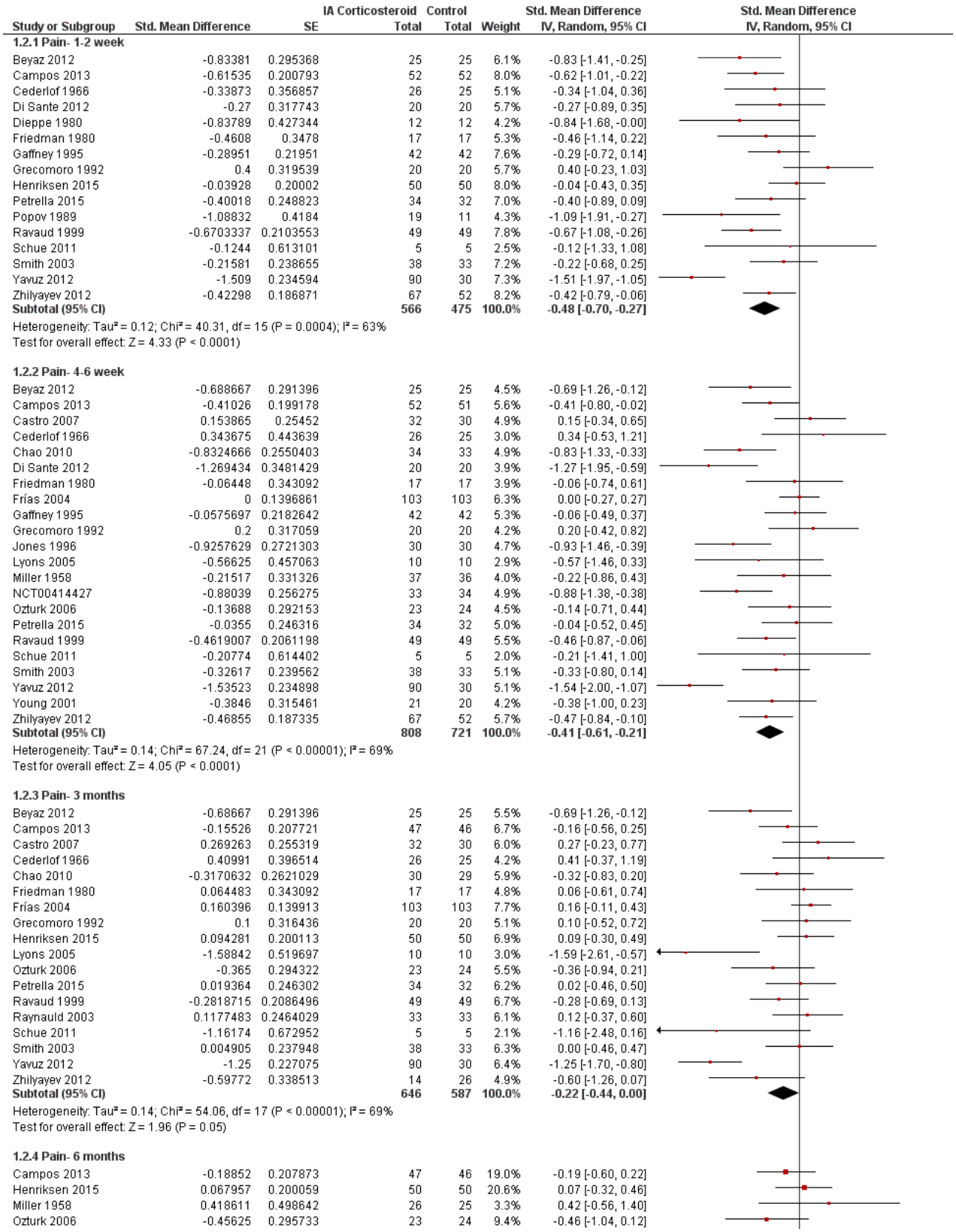


Figure 5. (Continued)

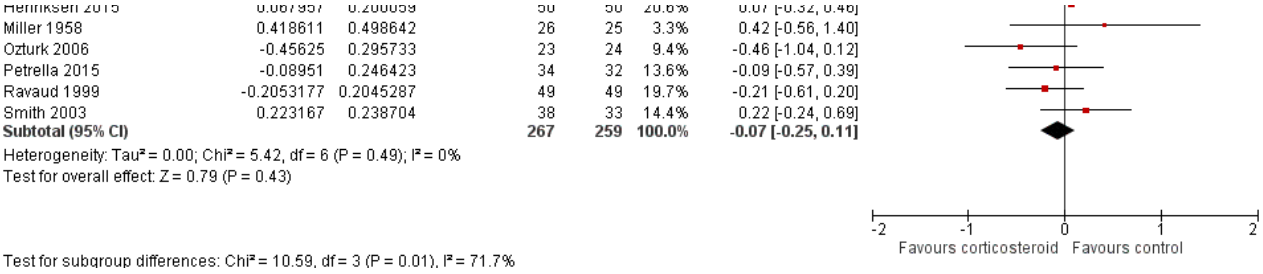


Table 1 presents the results of stratified analyses. We found little or no evidence for an association of SMDs with corticosteroid dosages, ultrasound guidance, local anesthetic, crystalline preparation, type of control intervention, financial support, publication type, concealment of allocation, adequate blinding of participants or therapists, or intention-to-treat analysis (P ≥ 0.10). There was some evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P = 0.05), or in trials that used viscosupplementation as a co-intervention (P = 0.08). There was strong evidence of lower treatment effects in trials that randomised on average at least 100 participants per group (P = 0.013), or in trials that used joint lavage as a co-intervention (P ≤ 0.001).

Knee function

Figure 6 presents results of the overall analysis of knee function reported closest to four to six weeks after end of treatment. Corticosteroids were more effective in function improvement than control interventions (SMD -0.33, 95% CI -0.56 to -0.09), which corresponds to a difference in functions scores of -0.7 units on standardised WOMAC disability scale ranging from 0 to 10. This corresponds to a difference in improvement of 13% (95% CI 4% to 22%) between corticosteroids and sham injection (Summary of findings for the main comparison), which translates into a NNTB to cause one additional treatment response on function of 10 (95% CI 7 to 33) (Summary of findings for the main comparison). An I^2 statistic of 69% indicated a moderate to large degree of between-trial heterogeneity (P for heterogeneity < 0.001). A visual inspection of the funnel plot suggested asymmetry (asymmetry coefficient -4.07, 95% CI -8.08 to -0.05), and the test for asymmetry showed evidence for asymmetry (P = 0.047) (Figure 7).

Figure 6. Forest plot of comparison: 2 Function, outcome: 2.1 Function - Main.

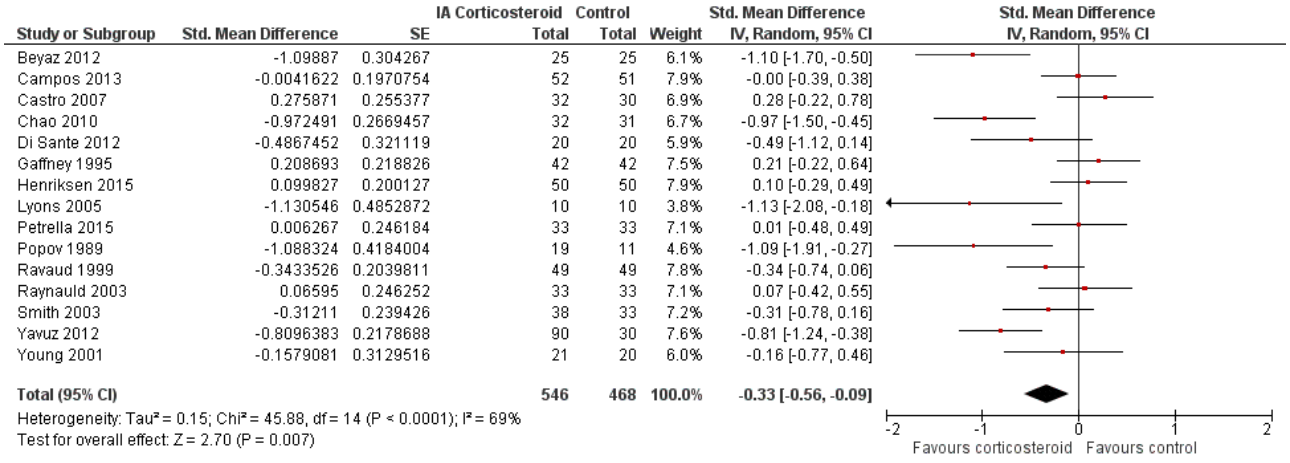


Figure 7. Contour-enhanced funnel plot for effects on knee function. Numbers on x axis refer to standardised mean differences (SMDs), on y axis to standard errors of SMDs

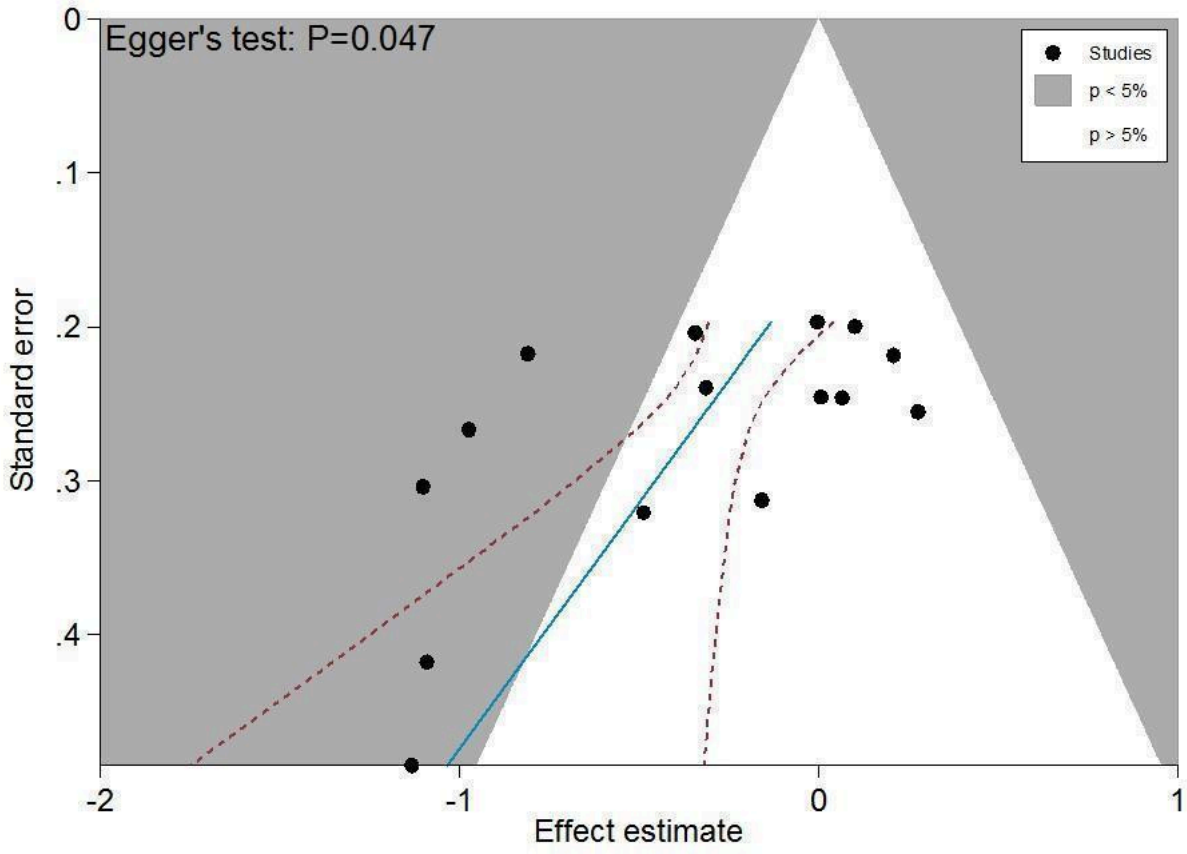


Figure 8 presents results stratified according to length of follow-up. Benefits were small to moderate at 1 to 2 weeks after end of treatment (SMD -0.43, 95% CI -0.72 to -0.14), small at 4 to 6 weeks (SMD -0.36, 95% CI -0.63 to -0.09), no effect at 13 weeks (SMD -0.13, 95% CI -0.37 to 0.10), and no effect at 26 weeks (SMD 0.06, 95% CI -0.16 to 0.28). An I^2 statistic of ≥ 62% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity ≤ 0.004), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P = 0.52).

Figure 8. Forest plot of comparison: 2 Function, outcome: 2.2 Function - Time points. P for trend = 0.011

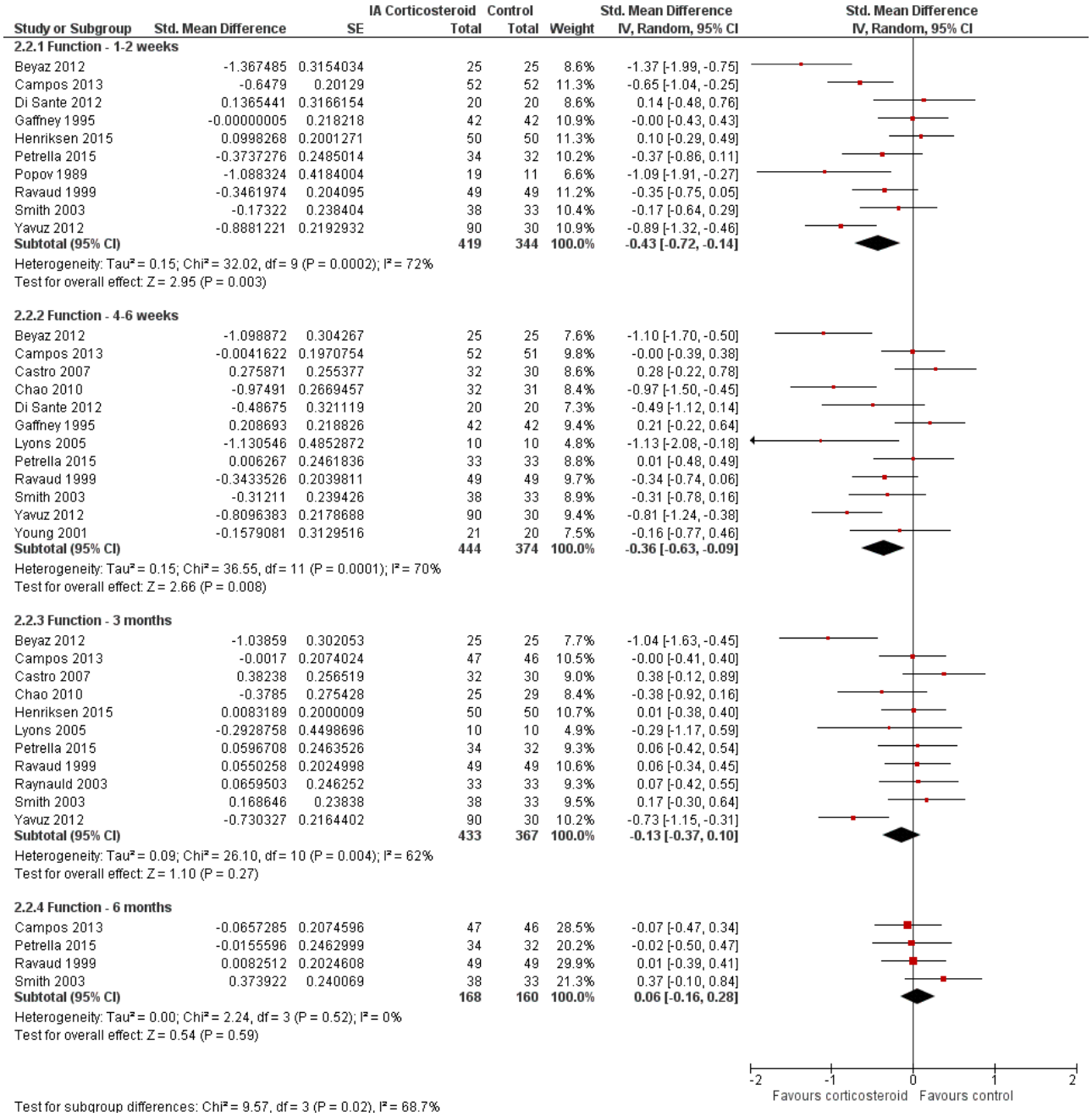


Table 2 presents the results of stratified analyses. We found little or no evidence for an association of SMDs with corticosteroid dosages, ultrasound guidance, local anaesthetic, crystalline preparation, joint lavage as a co-intervention, financial support, concealment of allocation, adequate blinding of participants or therapists, or intention-to-treat analysis (P ≥ 0.10). There was some evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P = 0.023), in unpublished trials (P = 0.023), in trials that used no intervention as control (P = 0.031), or in trials that used intra-articular viscosupplementation as a co-intervention (P = 0.06).

Secondary outcomes

Figure 9 presents results of the overall analysis on quality of life reported closest to four to six weeks after end of treatment. Corticosteroids had no effect on quality of life compared to control interventions (SMD -0.01, 95% CI -0.30 to 0.28). An I^2 statistic of 0% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.96). Figure 10 presents results of the overall analysis on joint space narrowing reported closest to four to six weeks after end of treatment. Corticosteroids had no effect in joint space narowing compared to control interventions (SMD -0.02, 95% CI -0.49 to 0.46). An I^2 statistic was not estimable because only one trial was included in this analysis. There was not enough data to

report results according to the pre-specified time points neither for quality of life nor joint space narrowing outcomes.

Figure 9. Forest plot of comparison: 3 Quality of life, outcome: 3.1 Quality of life - Main.

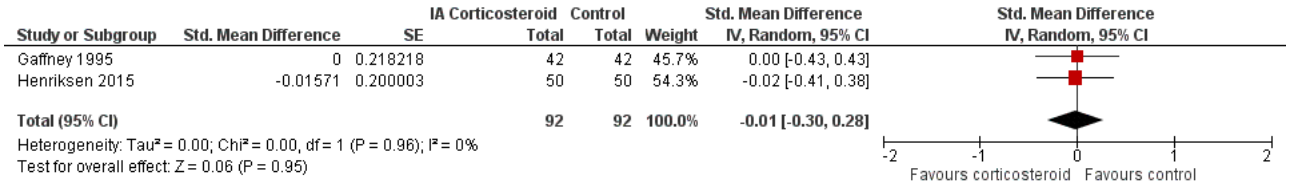


Figure 10. Forest plot of comparison: 7 Joint space narrowing, outcome: 7.1 Joint space narrowing - Main.

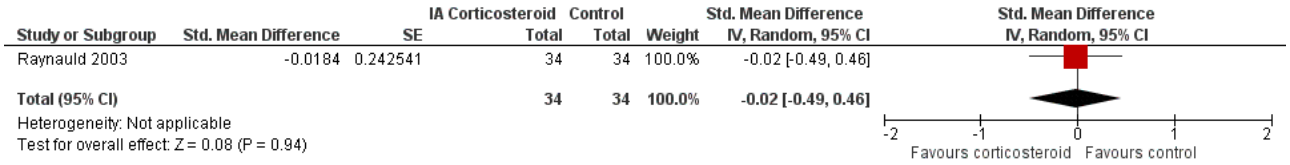


Figure 11 presents results of the overall analysis on number of participants experiencing any type of adverse event. We included 2 trials with a total of 84 participants and 46 events in this analysis. Participants on corticosteroids were 11% less likely to experience adverse events, but confidence intervals included the null effect (RR 0.89, 95% CI 0.64 to 1.23). An I^2 statistic of 0% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.44). Due to the imprecision in results, we were not able to calculate meaningful NNTHs.

Figure 11. Forest plot of comparison: 4 Number of participants experiencing any adverse event, outcome: 4.1 Number of participants experiencing any adverse event - Main.

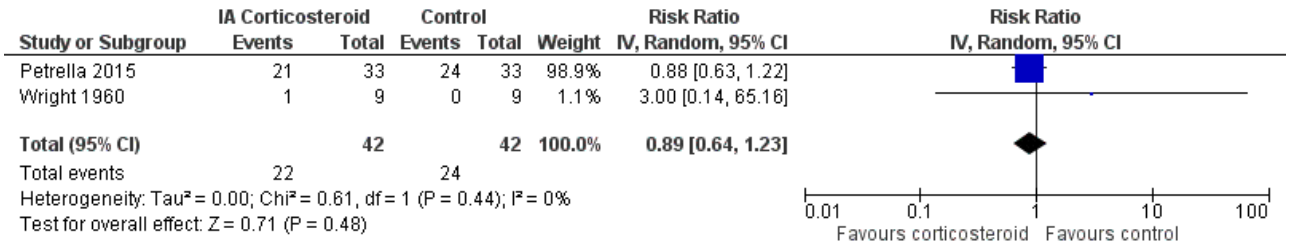


Figure 12 presents results of the overall analysis on number of participants who withdraw because of adverse events. We included 2 trials with a total of 204 participants and 5 events in this analysis. Participants on corticosteroids were 67% less likely to withdraw because of adverse events, but confidence intervals were wide and included the null effect (RR 0.33, 95% CI 0.05 to 2.07). An I^2 statistic of 0% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 1.00). Due to the imprecision in results, we were not able to calculate meaningful NNTHs.

Figure 12. Forest plot of comparison: 5 Number of participants who withdraw because of adverse events, outcome: 5.1 Number of participants who withdraw because of adverse events -Main.

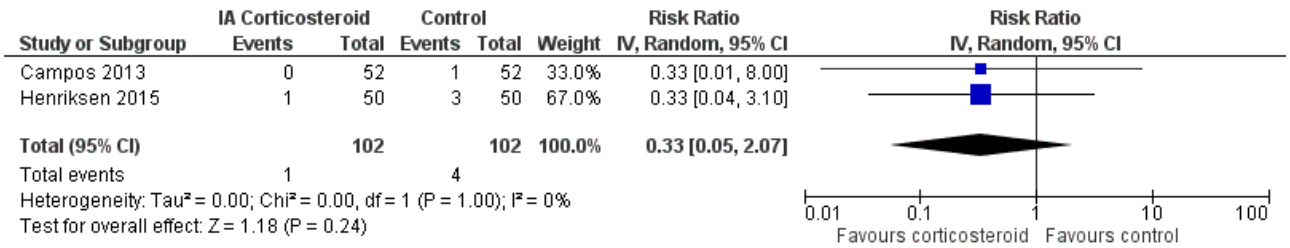
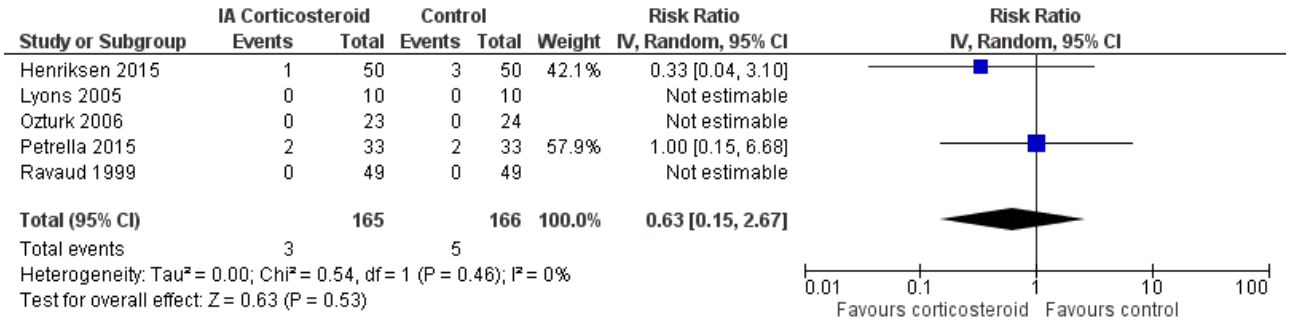


Figure 13 presents results of the overall analysis on number of participants experiencing serious adverse events. We included 5 trials with a total of 331 participants and 8 events in this analysis. Participants on corticosteroids were 27% less likely to withdraw because of adverse events, but confidence intervals were wide and included the null effect (RR 0.63, 95% CI 0.15 to 2.67). An I^2 statistic of 0% indicated a low degree of between-trial heterogeneity (P for heterogeneity = 0.46). Due to the imprecision in results, we were not able to calculate meaningful NNTHs.

Figure 13. Forest plot of comparison: 6 Number of participants experiencing any serious adverse event, outcome: 6.1 Number of participants experiencing any serious adverse event - Main.



Quality of the evidence (GRADE)

We graded the quality of the evidence as 'low' for all outcomes because treatment effect estimates were inconsistent with great variation across trials, pooled estimates were imprecise and did not rule out relevant or irrelevant clinical effects, and because most trials had a high or unclear risk of bias.

DISCUSSION

Summary of main results

In this update of the systematic review and meta-analysis by Bellamy (Bellamy 2006), we found most of the identified trials that compared intra-articular corticosteroids with sham or non-intervention control to be small and hampered by low methodological quality, and graded the quality of evidence for the major outcomes as 'low'. Only one trial was considered large according to our prespecified criteria (Frías 2004), with an average sample size of 100 participants or more per group, but this trial did not report adequate randomisation, participant blinding, or an intention-to-treat analysis. Conversely, only one trial reported adequate randomisation, participant blinding, and an intention-to-treat analysis (Henriksen 2015), but it was of moderate size only. An analysis of multiple time points suggested that effects decrease over time (P ≤ 0.011), and our analysis provides no evidence that an effect remains six months after a corticosteroid injection. Whether there are clinically important benefits after one to six weeks remains unclear in view of the overall quality of the evidence. A single trial included in this review described adequate measures to consistently minimise biases (Henriksen 2015); this trial did not find any benefit of intra-articular corticosteroids (SMD 0.04, 95% CI -0.43 to 0.35).

Quality of the evidence

The overall analyses of pain and function were difficult to interpret in view of the large extent of heterogeneity between trials. Stratified analyses suggested an association of estimates of treatment effects with sample size (P ≤ 0.05), and funnel plots appeared asymmetrical, even though the accompanying asymmetry test was positive only for function (P = 0.047). Stratified analyses according to components of methodological quality showed negative interaction tests. Conversely, trials with protocol-mandated concomitant lavage or viscosupplementation treatment in both experimental and control groups appeared to show smaller benefits of corticosteroids as compared with control.

The largest trial used joint lavage as concomitant treatment in all participants (Frías 2004). It therefore ultimately remains unclear whether the lack of treatment effect in this trial is a function of study size in the presence of small-study effects (Nüesch 2010), or a function of the concomitant use of joint lavage, which may act as an effect modifier even in the absence of a specific therapeutic effect (Reichenbach 2010). However, among the three largest trials, which included at least 50 participants per group, only one used lavage (Frías 2004), another used viscosupplementation as concomitant treatment (Campos 2013), and the third used neither (Henriksen 2015). When pooling these moderate-to-large trials, we found only a small, clinically irrelevant, and statistically non-significant effect on pain and function with a low degree of heterogeneity.

For other clinical characteristics including the use of ultrasound to guide injections, crystalline preparations, and prednisone equivalent doses, we did not find a treatment by subgroup interaction. Only two trials used ultrasound guidance to ensure proper placement of needles (Di Sante 2012, Henriksen 2015), however contradictory results and insufficient data are available to determine whether ultrasound guidance is associated with larger treatment effects.

Potential biases in the review process

We based our review on an extensive literature search, and so it seems unlikely that we missed relevant trials, provided that they were published as full-text articles or accessible in conference proceedings or trial registries (Egger 2003). Two review authors independently performed selection of trials and data extraction in order to reduce bias and transcription errors (Egger 2001; Gøtzsche 2007). We are therefore confident that potential biases during the review process were minimised.

Agreements and disagreements with other studies or reviews

Our update of the previous systematic review and meta-analysis by Bellamy identified 14 new trials that compared intra-articular corticosteroids with sham or non-intervention control (Bellamy 2006). In view of the overall body of evidence, we are as confident as Bellamy et al that no effect of intra-articular corticosteroids remains after six months, but are less confident than Bellamy that there is a clinically relevant short-term effect in view of large heterogeneity and possible small-study effects.

The most recent systematic review and network meta-analysis on intra-articular corticosteroids in knee osteoarthritis (Bannuru 2015), carried out in August 2014, identified seven trials comparing intra-articular corticosteroids to intra-articular placebo, all of which we included in our analysis. Again, we are less confident than these authors that there is a clinically relevant short-term effect of intra-articular corticosteroids considering the issues described above.

AUTHORS' CONCLUSIONS

Implications for practice

It remains unclear whether there are clinically important benefits one to six weeks after corticosteroid injection in view of the low quality of the included trials, the large amount of heterogeneity, and the likely presence of small-study effects (Nüesch 2010). Intra-articular corticosteroids should therefore be considered experimental in knee osteoarthritis and not be routinely used until adequately powered and properly designed trials clearly indicate a short- to mid-term benefit.

Implications for research

An adequately designed, multicentre, randomised, double-blind, sham-controlled, parallel-group trial is required to confirm or refute clinically relevant short- to mid-term benefits of intra-articular corticosteroids in knee osteoarthritis. A sample size of 100 participants per group would yield 80% power to detect a clinically meaningful moderate effect size of 0.4 standard deviation units in terms of pain reduction. The trial should use ultrasound guidance to ensure intra-articular needle placement as recently described by Henriksen et al (Henriksen 2015).

ACKNOWLEDGEMENTS

We acknowledge Dr. med. Marcello Di Nisio for his contribution with reference screening. We are grateful to Dr. Janne Estill and Elena Jüni for their translation of the Popov 1989 trial. We would also like to acknowledge the authors of the original version of this review: Nicholas Bellamy, Jane Campbell, Vivian Welch, Travis L Gee, Robert Bourne, and George A Wells.

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References to studies included in this review

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Campos 2013 *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beyaz 2012

Methods	Randomised controlled trial 3-arm parallel-group design Trial duration: 12 weeks
Participants	82 participants with knee osteoarthritis were randomised 73 participants were reported at baseline Number of females: 59 of 73 (81%) Mean age: 69.1 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide (1 ml) plus 20 mg bupivacaine (4 ml), single intra-articular injection *Control intervention* 1 ml saline plus 20 mg bupivacaine (4 ml), single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC pain Extracted function outcome: WOMAC function Maximum follow-up: 12 weeks
Notes	Funding: Boztepe State Hospital, Ordu, Republic of Turkey
Risk of bias	

Bias	Authors' judgement	Support for judgement

Beyaz 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized by the closed-envelope technique into three groups". Because the "closed-envelope technique" was not further specified, the risk of selection bias was considered unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized by the closed-envelope technique into three groups". Because the "closed-envelope technique" was not further specified, the risk of selection bias was considered unclear
Blinding of participants?	Low risk	Quote: "Since the solutions were in different colors, sticker was used to cover injectors to hide to ensure blinding."
Blinding of health care provider(s)	Low risk	Quote: "Injections were administered by another blinded investigator."
Intention-to-treat analysis performed? Pain	High risk	9 out of 82 participants were excluded because (quote) "they did not come for follow-up"
Intention-to-treat analysis performed? Function	High risk	9 out of 82 participants were excluded because (quote) "they did not come for follow-up"

Campos 2013

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 24 weeks
Participants	104 participants with knee osteoarthritis were randomised 104 participants were reported at baseline Number of females: 79 out of 104 (76%) Mean age: 63.0 years
Interventions	*Experimental intervention* 20 mg triamcinolone hexacetonide (1 ml) plus 6 ml hylan GF-20, single intra-articular injection *Control intervention* 6 ml hylan GF-20 intra-articularly, single intra-articular injection Quote: "Patients with bilateral disease had both knees treated with the same drug, but only one knee (reported by the patient as the worst) was included in the study"
Outcomes	Extracted pain outcome: WOMAC Pain Extracted function outcome: WOMAC Global Maximum follow-up: 24 weeks
Notes	Funding: São Paulo Research Foundation (FAPESP) (Sao Paulo, Brazil)

Risk of bias

Bias	Authors' judgement	Support for judgement

Campos 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a computer-generated program (available at: http://www.randomization.com/)."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Low risk	Quote: "Patients were blinded (blocked from watching the procedures by the use of a windscreen sunshade and did not know to which group they were assigned)."
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	High risk	5 of 52 participants excluded in experimental group, 6 of 52 participants excluded in control group
Intention-to-treat analysis performed? Function	High risk	5 of 52 participants excluded in experimental group, 6 of 52 participants excluded in control group

Castro 2007

Methods	Randomised controlled trial 5-arm parallel-group design Trial duration: 12.9 months
Participants	150 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: 115 Mean age: 65.4
Interventions	*Experimental intervention* Triamcinolone acetonide (no dosage or unit specified) + joint lavage, single intra-articular application *Control intervention* Joint lavage, single intra-articular application
Outcomes	Extracted pain outcome: WOMAC Pain Extracted function outcome: WOMAC Function Maximum follow-up: 12.9 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear

Castro 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis
Intention-to-treat analysis performed? Function	Low risk	All randomised participants included in the analysis

Cederlof 1966

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 8 weeks
Participants	51 injections in 44 knees belonging to 44 participants with knee osteoarthritis were randomised Unclear number of participants reported at baseline Number of females: 41 of 44 (93.2%) Mean age: Not reported
Interventions	*Experimental intervention* 50 mg prednisolone acetate (2 ml), single intra-articular injection *Control intervention* 2 ml physiologic saline, single intra-articular injection
Outcomes	Extracted pain outcome: Patient global assessment
Notes	Funding: Aktiebolaget Ferrosan, Malmö, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The out-patient department nurse decided which fluid was to be injected by tossing a coin"
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear

Cederlof 1966 *(Continued)*

Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis
Intention-to-treat analysis performed? Function	Unclear risk	Did not report extractable function outcome data

Chao 2010

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 12 weeks
Participants	79 participants with knee osteoarthritis were randomised 79 participants were reported at baseline Number of females: 2 of 79 (2.5%) Mean age: 64.3 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide (1 ml), single intra-articular injection *Control intervention* 1 ml 0.9% saline, single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Pain Extracted function outcome: WOMAC Global Maximum follow-up: 12 weeks
Notes	Funding: National Skeletal Muscle Research Center, NIH Grant HD050837

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Low risk	Quote: "Patients and assessors were blinded to treatment status" "Patients were then randomized to receive an injection of either (...) triamcinolone acetonide or (...) saline, which were drawn into a syringe covered with opaque tape prior to the patient encounter."
Blinding of health care provider(s)	High risk	Quote: "Injections were given (...) by a non-blinded physician"
Intention-to-treat analysis performed? Pain	High risk	9 of 40 participants excluded in experimental group, 9 of 39 participants excluded in control group

Chao 2010 *(Continued)*

Intention-to-treat analysis performed? Function	High risk	9 of 40 participants excluded in experimental group, 9 of 39 participants excluded in control group

Di Sante 2012

Methods	Randomised controlled trial 3-arm parallel-group design Trial duration: 4 weeks
Participants	60 participants with knee osteoarthritis were randomised 60 participants were reported at baseline Mean age: 70.6
Interventions	*Experimental interventions* 40 mg methylprednisolone acetate and lidocaine hydrochloride, single intra-articular injection + Horizontal therapy* locally (10 times over 2 weeks, each lasting 30 minutes) *Control intervention* Horizontal therapy* locally (10 times over 2 weeks, each lasting 30 minutes) Treatment duration: 4 weeks *Horizontal therapy was described as (quote): "Placement of 4 cutaneous electrodal pads (8 x 13 cm), one in center of the popliteal, one on the patella and two others at the posterior proximal site of the thighs, with a stimulation frequency oscillating at 100 Hz between 4400 and 12346 Hz for 30 minutes" Maximum follow-up: 4 weeks
Outcomes	Extracted pain outcome: Pain overall Extracted function outcome: WOMAC Function Maximum follow-up: 4 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "(...) using a computer generated 1:1:1 allocation sequence."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	High risk	No intra-articular sham injection in the placebo group (local therapy only)
Blinding of health care provider(s)	High risk	No intra-articular sham injection in the placebo group (local therapy only)

Di Sante 2012 *(Continued)*

Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis
Intention-to-treat analysis performed? Function	Low risk	All randomised participants included in the analysis

Dieppe 1980

Methods	Randomised controlled trial 2-arm cross-over design Trial duration: 2 weeks
Participants	24 knees belonging to 16 participants with knee osteoarthritis were randomised 24 knees belonging to 16 participants were reported at baseline Mean age: 65 Number of females: 13 out of 16 (81%)
Interventions	*Experimental intervention* 20 mg triamcinalone hexacetonide (1 ml), single intra-articular injection *Control intervention* 1 ml of saline, single intra-articular injection Cross-over after 1 week. Every participant received 1 injection (experimental and control) each
Outcomes	Extracted pain outcome: Pain overall Maximum follow-up: 1 week
Notes	2 trials were reported in the same paper. Trial A did not report pain outcomes seperately for treatment and intervention and was excluded. Trial B was included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	High risk	Quote: Described as "single-blind, blind-observer", implying that participants were not blinded
Blinding of health care provider(s)	High risk	Quote: Described as "single-blind, blind-observer", implying that healthcare providers were not blinded
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis

Dieppe 1980 *(Continued)*

Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Friedman 1980

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 8 weeks
Participants	34 participants with knee osteoarthritis were randomised 34 participants were reported at baseline Number of females: Not reported Mean age: 60.0 years
Interventions	*Experimental intervention* 20 mg triamcinolone hexacetonide, single intra-articular injection *Control intervention* "Polysorbate, sorbitol solution, benzyl alcohol and water", single intra-articular injection
Outcomes	Extracted pain outcome: Pain overall Maximum follow-up: 8 weeks
Notes	Funding: Grant from the Eastern Pennsylvania Chapter of the Arthritis Foundation and by the Philadelphia Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not clearly reported, so the risk of selection bias was unclear. Quote: "Half of the patients, selected according to a predetermined random schedule, were treated (...)."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Low risk	Quote: "During the time of [the injection] (...), the physician and patient were positioned so that neither could see the nurse's face nor the material she injected. Thus, neither had any direct information concerning what was injected and, practically speaking, had no contact with the only person who knew"
Blinding of health care provider(s)	Low risk	Quote: "The physician-experimenter performed the arthrocentesis (...) a nurse-assistant entered the room and performed the injection through the intraarticular needle, and left the room. During the time of this taking place, the physician and patient were positioned so that neither could see the nurse's face nor the material she injected. Thus, neither had any direct information concerning what was injected and, practically speaking, had no contact with the only person who knew"

Friedman 1980 *(Continued)*

Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis. Quote: "All patients were seen 1 wk, 4 wk, 6 wk and 8 wk post-injection except those whose pain scores at any subsequent evaluation were the same as their pre-treatment scores; they were not seen further. It was assumed that their scores would no longer improve and they were counted as remaining at their pre-treatment level throughout the experiment".
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Frías 2004

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 12 weeks
Participants	299 knees belonging to 205 participants with knee osteoarthritis were randomised 299 knees belonging to 205 participants were reported at baseline Number of females: 234 (78%) of 299 knees belonged to female participants Mean age: 67.0 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide plus lavage (3 L of cold (8°C) saline), single intra-articular application *Control intervention* Lavage (3 L of cold (8°C) saline), single intra-articular application
Outcomes	Extracted pain outcome: Pain overall Maximum follow-up: 12 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	Although the authors stated "Glucocorticoid treatment with triamcinolone acetonide was always given on a blind basis", they also stated that this was an open trial (Quote: "The study was of the longitudinal, open, prospective, controlled type").The risk of performance bias was therefore considered unclear
Blinding of health care provider(s)	Unclear risk	Although the authors stated "Glucocorticoid treatment with triamcinolone acetonide was always given on a blind basis", they also stated that this was an

Frías 2004 *(Continued)*

		open trial (Quote: "The study was of the longitudinal, open, prospective, controlled type"). The risk of performance bias was therefore considered unclear
Intention-to-treat analysis performed? Pain	High risk	82 of 299 knees were excluded at 1 month, 51 of 299 knees were excluded at 3 months
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Gaffney 1995

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 6 weeks
Participants	84 participants with knee osteoarthritis were randomised 84 participants were reported at baseline Number of females: 60 out of 84 (71%) Mean age: 67.0 years
Interventions	*Experimental intervention* 20 mg triamcinolone hexacetonide (1 ml), single intra-articular injection *Control intervention* 1 ml of 0.9% normal saline, single intra-articular injection
Outcomes	Extracted pain outcome: Pain overall Extracted function outcome: Other function composite Maximum follow-up: 6 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Low risk	Quote: "Although this study was not, by strict definition, double-blinded, we attempted to ensure that patients were not aware of the treatment allocated to them, by shielding the identity of the treatment received from their view at the time of injection; only the injecting physician (IL) was aware of the nature of the injection administered."
Blinding of health care provider(s)	High risk	Quote: "Although this study was not, by strict definition, double-blinded, we attempted to ensure that patients were not aware of the treatment allocated

Gaffney 1995 *(Continued)*

		to them, by shielding the identity of the treatment received from their view at the time of injection; only the injecting physician (IL) was aware of the nature of the injection administered."
Intention-to-treat analysis performed? Pain	Unclear risk	2 of 42 participants in control group withdrew. It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	2 of 42 participants in control group withdrew. It was unclear whether all participants randomised were also analysed

Grecomoro 1992

Methods	Randomised controlled trial 2-arm cross-over design Trial duration: 8.6 weeks
Participants	40 participants with knee osteoarthritis were randomised 40 participants were reported at baseline Number of females: 27 out of 40 (67.5%) Mean age: 42.3 years
Interventions	*Experimental intervention* 0.4 mg dexamethasonephosphate plus 20 mg sodium hyaluronate in 2 ml phosphate buffer, 5 intra-articular injections, 1 weekly for 5 weeks *Control intervention* 20 mg sodium hyaluronate in 2 ml phosphate buffer, 5 intra-articular injections, 1 weekly for 5 weeks
Outcomes	Extracted pain outcome: Pain on activities other than walking Maximum follow-up: 8.6 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	High risk	Quote: "The trial design was open and randomized."
Blinding of health care provider(s)	High risk	Quote: "The trial design was open and randomized."
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis

Grecomoro 1992 *(Continued)*

Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Henriksen 2015

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 26 weeks
Participants	100 participants with knee osteoarthritis were randomised 100 participants were reported at baseline Number of females: 61 out of 100 (61%) Mean age: 63.4 years
Interventions	*Experimental intervention* 40 mg methylprednisolone acetate (1 ml) dissolved in 4 ml of lidocaine hydrochloride, single intra-articular injection + 12-week exercise program *Control intervention* 1 ml isotonic saline mixed with 4 ml of lidocaine hydrochloride, single intra-articular injection + 12-week exercise program
Outcomes	Extracted pain outcome: Other pain composite Extracted pain function: Other function composite Maximum follow-up: 26 weeks
Notes	Funding: Grants by: 10-093704 from the Danish Council for Independent Research Medical Science, Oak Foundation, Association of Danish Physiotherapists, Lundbeck Foundation, Capital Region of Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization sequence was produced before any patients were enrolled that allocated participants in permuted blocks of 2 to 6 to the corticosteroid or the placebo group (1:1)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence was prepared by a biostatistician with no clinical involvement in the trial (R.C.). The allocation was concealed in a password-protected computer file only accessible by the biostatistician. Individual allocations were held in sealed, opaque, consecutively numbered envelopes."
Blinding of participants?	Low risk	Quote: "To ensure blinding of the participants and the clinician performing the injections, the syringes were prepared by the study nurse in the absence of participants and blinded study staff. Because the corticosteroid liquid is milky white and the saline is clear, the syringes were masked with opaque tape to prevent disclosure of the content during the injection procedure."

Henriksen 2015 *(Continued)*

Blinding of health care provider(s)	Low risk	Quote: "To ensure blinding of the participants and the clinician performing the injections, the syringes were prepared by the study nurse in the absence of participants and blinded study staff. Because the corticosteroid liquid is milky white and the saline is clear, the syringes were masked with opaque tape to prevent disclosure of the content during the injection procedure."
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis
Intention-to-treat analysis performed? Function	Low risk	All randomised participants included in the analysis

Jones 1996

Methods	Randomised controlled trial 2-arm cross-over design Trial duration: 16 weeks
Participants	59 participants with knee osteoarthritis were randomised 59 participants were reported at baseline Number of females: 37 out of 59 (63%) Mean age: 70.6 years
Interventions	*Experimental intervention* 40 mg methyl prednisolone acetate (1 ml), single intra-articular injection *Control intervention* 1 ml 0.9% saline, single intra-articular injection Cross-over after 8 weeks. Every participant received 1 injection (experimental and control) each
Outcomes	Extracted pain outcome: Pain on activities other than walking Maximum follow-up: 8 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	Quote: "Each injection was given by a second operator, thus blinding both patient and assessor." No further description of blinding

Jones 1996 *(Continued)*

Blinding of health care provider(s)	Unclear risk	Quote: "Each injection was given by a second operator, thus blinding both patient and assessor." No further description of blinding
Intention-to-treat analysis performed? Pain	High risk	Quotes: "As some data was missing due to patient withdrawal, all analyses were performed on a last measures carried forward, intention to treat basis", but still not all participants randomised were analysed. Quote: "One patient failed to enter the study and received no injection, leaving 59 patients available for the analysis."
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Lyons 2005

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 8.6 weeks
Participants	20 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: 11 Mean age: 59.7
Interventions	*Experimental intervention* 80 mg methylprednisolone (2 ml) + 5 ml 1% lignocaine, single intra-articular injection *Control intervention* 10 ml of 1% lignocaine, single intra-articular injection
Outcomes	Extracted pain outcome: Pain overall Extracted function outcome: Global disability score Maximum follow-up: 8.6 weeks
Notes	Funding: West London Research Network, Primary Care Scientist Award funded by the Department of Health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind healthcare providers was appropriate

Lyons 2005 *(Continued)*

Blinding of health care provider(s)	High risk	Quote: "(The study) was single blind, with the principal investigator administering the treatment and also measuring outcome."
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis
Intention-to-treat analysis performed? Function	Low risk	All randomised participants included in the analysis

Miller 1958

Methods	Randomised controlled trial 5-arm parallel-group design Trial duration: 33.8 weeks
Participants	202 participants with knee osteoarthritis were randomised Unclear number of participants reported at baseline Number of females: 122 Mean age: not reported
Interventions	*Experimental intervention* 50 mg of hydrocortisone (2 ml) + 8 ml of physiological normal saline, 5 intra-articular injections, interval of 2 weeks *Control intervention* Physiological normal saline solution (no dosage), 5 intra-articular injections, interval of 2 weeks
Outcomes	Extracted pain outcome: Patients' global assessment Maximum follow-up: 25.8 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	High risk	21 of 202 participants were excluded

Miller 1958 *(Continued)*

Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

NCT00414427

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 12 weeks
Participants	79 participants with knee osteoarthritis were randomised 79 participants were reported at baseline Number of females: 3 out of 79 (4%) Mean age: 63.0 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide, single intra-articular injection *Control intervention* 0.9% saline (no dosage), single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Pain Maximum follow-up: 12 weeks
Notes	Funding: University of California, San Diego

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	It was unclear if method used to blind healthcare providers was appropriate
Intention-to-treat analysis performed? Pain	High risk	7 of 40 participants excluded in experimental group, 5 of 39 participants excluded in control group
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Ozturk 2006

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 52 weeks
Participants	47 participants with knee osteoarthritis were randomised 40 participants were reported at baseline Number of females: 39 out of 47 (83%) Mean age: 58.0 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide (1 ml) plus 2 ml sodium hyaluronate. Sodium hyaluronate was administered in 3 intra-articular injections in the first month and 3 intra-articular injections during the sixth month, triamcinolone acid was added prior to the first and fourth application. *Control intervention* 2 ml sodium hyaluronate, 3 intra-articular injections in the first month, and 3 intra-articular injections during the sixth month
Outcomes	Extracted pain outcome: WOMAC Pain Maximum follow-up: 25.9 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to one of the two treatment groups based on a table of randomly assorted digits: A and B."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if participants were blinded (trial described as "single blind" but no description of who was blinded)
Blinding of health care provider(s)	Unclear risk	It was unclear if healthcare providers were blinded (trial described as "single blind" but no description of who was blinded)
Intention-to-treat analysis performed? Pain	High risk	7 of 23 participants excluded in experimental group, 0 of 24 participants excluded in control group
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Petrella 2015

Methods	Randomised controlled trial 2-arm parallel-group design

Petrella 2015 *(Continued)*

	Trial duration: 26 weeks
Participants	98 participants with knee osteoarthritis were randomised 98 participants were reported at baseline Number of females: 56 out of 98 (57%) Mean age: 59.7 years
Interventions	*Experimental intervention* 10 mg triamcinolone acetonide + hyaluronan solution (no dosage stated), 6 ml total, single intra-articular injection *Control intervention* Hyaluronan solution (no dosage stated), single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Pain Extracted function outcome: WOMAC Function Maximum follow-up: 26 weeks
Notes	Funding: Carbylan Therapeutics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization treatment was computer generated and was stratified by study center."
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization treatment was computer generated and was stratified by study center."
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	High risk	Quote: "An injecting physician delivered the randomized treatment and remained unblinded."
Intention-to-treat analysis performed? Pain	High risk	2 of 33 participants excluded in experimental group, 1 of 33 participants excluded in control group
Intention-to-treat analysis performed? Function	High risk	2 of 33 participants excluded in experimental group, 1 of 33 participants excluded in control group

Popov 1989

Methods	Randomised controlled trial 5-arm parallel-group design Trial duration: 2.7 weeks
Participants	48 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline

Popov 1989 *(Continued)*

	Number of females: 38
	Mean age: 55 years
Interventions	*Experimental interventions*
	Intervention (A): 40 mg triamcinolone, 3 intra-articular injections, interval 1 week
	Intervention (B): 50 mg hydrocortisone, 3 intra-articular injections, interval 1 week
	Control intervention
	Saline solution (no dosage stated), 2 intra-articular injections, interval 1 week
Outcomes	Extracted pain outcome: (A)-(B): other algofunctional
	Extracted function outcome: (A)-(B): other algofunctional
	Maximum follow-up: 0.7 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	It was unclear if method used to blind healthcare providers was appropriate
Intention-to-treat analysis performed? Pain	Unclear risk	It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	It was unclear whether all participants randomised were also analysed

Ravaud 1999

Methods	Randomised controlled trial
	2 x 2 factorial design
	Trial duration: 24 weeks
Participants	98 participants with knee osteoarthritis were randomised
	98 participants were reported at baseline
	Number of females: 66 out of 98 (67%)
	Mean age: 65.4

Ravaud 1999 *(Continued)*

Interventions	*Experimental interventions* Intervention (A): 3.75 mg cortivazol (1.5 ml), single intra-articular injection Intervention (B): Lavage, single intra-articular application + 3.75 mg cortivazol (1.5 ml), single intra-articular injection *Control intervention* Intervention (A): 1.5 ml 0.9% normal saline, single intra-articular injection Intervention (B): Lavage, single intra-articular application
Outcomes	Extracted pain outcome: Pain overall Extracted function outcome: Lequesne index Maximum follow-up: 24 weeks
Notes	Funding: Société Française de Rhumatologie and the Direction de la Recherche Clinique (Assistance Publique - Hôpitaux de Paris)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	Quote: "The study was double-blind in relation to the IA corticosteroid and open with regard to joint lavage."
Blinding of health care provider(s)	Unclear risk	Quote: "The study was double-blind in relation to the IA corticosteroid and open with regard to joint lavage. However, the procedure (joint lavage and/or IA injection) was performed by a physician other than the blinded evaluator."
Intention-to-treat analysis performed? Pain	Low risk	All randomised participants included in the analysis. Quote: "The last observation–carried-forward procedure was used to adjust for missing values."
Intention-to-treat analysis performed? Function	Low risk	All randomised participants included in the analysis. Quote: "The last observation–carried-forward procedure was used to adjust for missing values."

Raynauld 2003

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 54 weeks
Participants	68 participants with knee osteoarthritis were randomised 68 participants were reported at baseline Number of females: 42 out of 68 (68%)

Raynauld 2003 *(Continued)*

	Mean age: 63.2 years
Interventions	*Experimental intervention* 40 mg triamcinolone acetonide (1 ml), 8 intra-articular injections, interval 3 months, over 21 months *Control intervention* 1 ml saline intra-articularly, 8 intra-articular injections, interval 3 months, over 21 months
Outcomes	Extracted pain outcome: WOMAC Pain. After end of treatment (during follow-up) Extracted function outcome: WOMAC Function. After end of treatment (during follow-up) Maximum follow-up: 12.9 weeks
Notes	Funding: Fonds de la recherche en santé du Québec

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to the IA steroid or IA saline group based on a table of randomly assorted digits."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	Study described as double-blind but no description of method of blinding provided
Blinding of health care provider(s)	High risk	Study described as double-blind. The following statements indicate that "double-blind" in this trial means that only patients and outcome assessors were blinded: "In order to preserve the blind, the injections were given by a rheumatologist (DC or BH) other than the evaluators." "Investigators performed these evaluations in a blinded manner using validated measures."
Intention-to-treat analysis performed? Pain	High risk	1 of 34 participants excluded in experimental group, 1 of 34 participants excluded in control group
Intention-to-treat analysis performed? Function	High risk	1 of 34 participants excluded in experimental group, 1 of 34 participants excluded in control group

Schue 2011

Methods	Randomised controlled trial 3-arm parallel-group design Trial duration: 8 weeks
Participants	16 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: not reported Mean age: not reported

Schue 2011 *(Continued)*

Interventions	*Experimental intervention* 80 mg methylprednisolone, single intra-articular injection *Control intervention* Saline (no dosage specified), single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Global Maximum follow-up: 8 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Unclear risk	It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

Smith 2003

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 24 weeks
Participants	77 participants with knee osteoarthritis were randomised 71 participants were reported at baseline Number of females: 27 out of 77 (35%) Mean age: 66.8 years
Interventions	*Experimental intervention* 120 mg methylprednisolone acetate following joint lavage, single intra-articular injection *Control intervention* Treatment duration: 1 day

Smith 2003 *(Continued)*

	Normal saline (no dosage) following joint lavage, single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Pain Extracted function outcome: WOMAC Function Maximum follow-up: 24 weeks
Notes	Funding: National Health and Medical Research Council (Australia) Arthritis Foundation of Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was computer-generated by a member of the hospital pharmacy department, who also prepared a blinded intra-articular injection"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was computer-generated by a member of the hospital pharmacy department, who also prepared a blinded intra-articular injection"
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	It was unclear if method used to blind healthcare providers was appropriate
Intention-to-treat analysis performed? Pain	High risk	Quote: "In the event of relapse as defined above, the last documented outcome variables were carried forward". Still, 6 participants were excluded (those needing surgical intervention because of the arthroscopic findings at baseline)
Intention-to-treat analysis performed? Function	High risk	Quote: "In the event of relapse as defined above, the last documented outcome variables were carried forward". Still, 6 participants were excluded (those needing surgical intervention because of the arthroscopic findings at baseline)

Wright 1960

Methods	Randomised controlled trial 3-arm parallel-group design Trial duration: 20 weeks
Participants	38 knees belonging to 25 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: not stated Mean age: not stated
Interventions	*Experimental intervention* Intervention (A): 25 mg hydrocortisone acetate (1 ml), 4 intra-articular injections, interval 2 weeks over 6 weeks Intervention (B): 25 mg hydrocortisone tertiary-butylacetate (1 ml), 4 intra-articular injections, interval 2 weeks over 6 weeks

Wright 1960 *(Continued)*

	Control intervention
	1 ml of placebo, 4 intra-articular injections, interval 2 weeks over 6 weeks
	Cross-over design, every participant received 3 x 4 injections
Outcomes	Only information on adverse events was extracted
Notes	There was no extractable data on pain or function

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The order of courses in each patient was randomized from a master sheet in which names were entered consecutively."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Unclear risk	Did not report extractable pain outcome data
Intention-to-treat analysis performed? Function	Unclear risk	Did not report extractable function outcome data excluded in control group

Yavuz 2012

Methods	Randomised controlled trial
	4-arm parallel-group design
	Trial duration: 12 weeks
Participants	120 participants with knee osteoarthritis were randomised
	120 participants were reported at baseline
	Number of females: 76 out of 120 (63%)
	Mean age: 60.0 years
Interventions	*Experimental intervention*
	Intervention (A): 40 mg triamsinolon acetonate (1 ml), single intra-articular injection
	Intervention (B): 3 mg betametazone disodium phosphate (1 ml), single intra-articular injection
	Intervention (C): 40 mg methylprednisolone acetate (1 ml), single intra-articular injection
	Control intervention
	1 ml 0.9% sodium chloride, single intra-articular injection

Yavuz 2012 *(Continued)*

Outcomes	Extracted pain outcome (A)-(C): Pain overall Extracted function outcome (A)-(C): Lequesne index Maximum follow-up: 12 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "A total of 120 eligible patients with knee osteoarthritis were included (according to their admission date) and randomized into four groups."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if participants were blinded
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Unclear risk	It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	It was unclear whether all participants randomised were also analysed

Young 2001

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 4.3 weeks
Participants	41 knees belonging to 40 participants with knee osteoarthritis were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: 16 Mean age: 66.5 years
Interventions	*Experimental intervention* 120 mg methylprednisolone acetate, single intra-articular injection *Control intervention* Normal saline (no dosage stated), single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Global Extracted function outcome: Other function composite Maximum follow-up: 4.3 weeks

Young 2001 *(Continued)*

Notes	Funding: National Health and Medical Research Council, The Clive and Vera Ramaciotti Trust, The Rebecca L. Cooper Foundation, University of New South Wales, The Arthritis Foundation of Australia, The Royal Australasian College of Physicians

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence of allocation was not reported, so the risk of selection bias was unclear
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the random sequence of allocation was not reported, so the risk of selection bias was unclear
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Unclear risk	It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	It was unclear whether all participants randomised were also analysed

Zhilyayev 2012

Methods	Randomised controlled trial 4-arm parallel-group design Trial duration: 12 weeks
Participants	209 knees belonging to 112 participants were randomised Unclear number of participants with knee osteoarthritis reported at baseline Number of females: not stated Mean age: not stated
Interventions	*Experimental intervention* 20 mg triamcinolone acetonid plus 10 ml 0.5% procaine, single intra-articular injection *Control intervention* 10 ml 0.5% procaine, single intra-articular injection
Outcomes	Extracted pain outcome: WOMAC Pain Maximum follow-up: 12 weeks
Notes	

Risk of bias

Zhilyayev 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "joints were randomized by envelopes to one of 4 treatments"
Allocation concealment (selection bias)	Unclear risk	Quote: "joints were randomized by envelopes to one of 4 treatments"
Blinding of participants?	Unclear risk	It was unclear if method used to blind participants was appropriate
Blinding of health care provider(s)	Unclear risk	Physicians were not explicitly described as blinded, so the risk of performance bias was unclear
Intention-to-treat analysis performed? Pain	Unclear risk	It was unclear whether all participants randomised were also analysed
Intention-to-treat analysis performed? Function	Unclear risk	Not applicable, no function outcome reported

IA: intra-articular
WOMAC: Western Ontario and McMaster Universities Arthritis Index

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

Study	Reason for exclusion
Abdulla 2013	Recent systematic review
Anonymous 1978	Wrong study design
Anonymous 2011	Wrong study design
Arroll 2004	Recent systematic review
Arroll 2005	Wrong study design
Avouac 2010	Recent systematic review
Baker 1969	Active comparator
Bannuru 2013	Wrong study design: Abstract to relevant systematic review, no references listed
Bannuru 2014	Wrong study design: Abstract to relevant systematic review, no references listed
Bannuru 2015	Recent systematic review
Baratham 2010	Wrong outcomes
Bellamy 2005	Recent systematic review
Bellamy 2006	Recent systematic review
Bennell 2012	Wrong study design
Bjordal 2007	Recent systematic review

Study	Reason for exclusion
Blanke 2008	Wrong study design
Bourne 1985	Wrong study design
Brys 2004	Wrong study design
Canillas 2011	Wrong study design
Cats 1979b	Wrong study population
Charalambous 2004	Wrong study design
Cheng 2012	Recent systematic review
Courtney 2009	Wrong study design
Douglas 2012	Wrong study design
Gait 2014	Wrong study design
Garg 2013	Wrong study design: Abstract to relevant systematic review , no references listed
Garg 2014	Reason for exclusion
Gerlag 2008a	Wrong study design
Godwin 2004	Recent systematic review
Habib 2009	Wrong study design
Habib 2010	Wrong study design
Hepper 2009	Reason for exclusion
Hirsch 2013	Reason for exclusion
Ivanov 1981	Wrong comparator
Jarner 1992	Active comparator
Jones 1993	Wrong study design
Jones 2014	Wrong study design
Keagy 1967	Wrong study design
Khitrov 1997	Active comparator
Kizilkaya 2004	Postsurgical setting
Kizilkaya 2005	Postsurgical setting
Koyonos 2009	Postsurgical setting

Study	Reason for exclusion
Krause 1971	Wrong study design
Legre-Boyer 2015	Wrong study design
Lequesne 1970	Wrong study design
Maricar 2013	Wrong study design: Abstract to relevant systematic review , no references listed
Maricar 2013c	Recent systematic review
Maricar 2014	Wrong study design
McAlindon 2014	Wrong study design
Murdoch 1959	Wrong study design
Murdoch 1959a	Wrong study design
Neame 2003	Wrong study design
Nicol 1972	Wrong study design
No named author	Wrong study design
No named author a	Wrong study design
No named author b	Wrong study design
No named author c	Wrong study design
Parmigiani 2010	Duplicate reference
Pendleton 2008	Wrong study design
Punzi 2001	Wrong intervention
Rasmussen 1998	Postsurgical setting
Rasmussen 1998a	Postsurgical setting
Rasmussen 1998b	Postsurgical setting
Reshetov 2000	Wrong comparator
Ronchetti 2001	Active comparator
Roskos 2005	Wrong study design
Saito 1971	Wrong study design
Shah 1967	Wrong comparator
Sheldon 1973	Wrong study population

Study	Reason for exclusion
Stein 1996	Active comparator
Stitik 2006	Wrong study design
Stojanovic 1969	Wrong study design
Talke 1986	Wrong study design
Van Middelkoop 2013	Wrong study design: Abstract to relevant systematic review , no references listed
Van Middelkoop 2013a	Wrong study design: Abstract to relevant systematic review , no references listed
Van Middelkoop 2013b	Wrong study design
Van Middelkoop 2014	Wrong study design: Abstract to relevant systematic review , no references listed
Van Middelkoop 2014a	Wrong study design: Abstract to relevant systematic review , no references listed
Wang 1998	Postsurgical setting
Wang 2015	Wrong study design
Wramner 1959	Wrong study design
Yamamoto 1970	Wrong study design
Zhang 2008	Wrong study design
Zhang 2010	Wrong study design
Zuckner 1958	Active comparator

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ellis 2011

Methods	Randomised controlled trial 2-arm parallel-group design Trial duration: 12 weeks
Participants	16 participants with knee osteoarthritis were randomised
Interventions	*Experimental intervention* 3-month exercise program plus 40 mg triamcinolone mixed with 4 ml 1% lidocaine, single intra-articular injection *Control intervention*

Ellis 2011 *(Continued)*

	3-month exercise program plus 1 ml normal saline mixed with 4 ml 1% lidocaine, single intra-articular injection
Outcomes	Maximum follow-up: 12 weeks Outcome data (KOOS pain and function, WOMAC pain and function) not extractable
Notes	

Friedman 1978

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Outcome data not extractable
Notes	

Hall 2013

Methods	Randomised controlled trial 2-arm parallel-group design
Participants	25 participants with knee osteoarthritis were randomised
Interventions	*Experimental intervention* 40 mg methylprednisolone acetate, single intra-articular injection *Control intervention* saline, single intra-articular injection Cross-over design: Every participant received 1 injection each
Outcomes	Maximum follow-up: 1 week Outcome data (WOMAC pain, pain overall, ICOAP questionnaire, ultrasound examination) not extractable
Notes	

Hall 2014

Methods	Randomised controlled trial 2-arm parallel-group design
Participants	25 participants with knee osteoarthritis were randomised

Hall 2014 *(Continued)*

Interventions	*Experimental intervention* 40 mg methylprednisolone acetate, single intra-articular injection *Control intervention* saline, single intra-articular injection Cross-over design: Every participant received 1 injection each
Outcomes	Maximum follow-up: 1 week Outcome data (WOMAC pain, pain overall, ICOAP questionnaire, ultrasound examination) not extractable
Notes	

Motyl 2013

Methods	Measurement reliability study on participants later taking part in a randomised controlled trial for intra-articular corticosteroid injection in knee osteoarthritis
Participants	15 participants with knee osteoarthritis
Interventions	Unclear Data for the study was collected before the intra-articular injection
Outcomes	Outcome data not extractable
Notes	

Motyl 2013a

Methods	Measurement reliability study on participants later taking part in a randomised controlled trial for intra-articular corticosteroid injection in knee osteoarthritis
Participants	15 participants with knee osteoarthritis
Interventions	Unclear Data for the study was collected before the intra-articular injection
Outcomes	Outcome data not extractable
Notes	

O'Neill 2014

Methods	Open-label clinical trial
Participants	100 participants with knee osteoarthritis

O'Neill 2014 *(Continued)*

Interventions	*Experimental intervention* Corticosteroid, single intra-articular injection, type and dosage of corticosteroid unclear. The study analysed the changes in MRI scans before and after the intra-articular corticosteroid injection. All participants received the experimental intervention, there was no control group.
Outcomes	Outcome data not extractable
Notes	

Raynauld 1999

Methods	Randomised controlled trial 2-arm parallel-group design
Participants	80 participants with knee osteoarthritis were randomised
Interventions	*Experimental intervention* 40 mg triamcinolone hexacetonide, 8 intra-articular injections, 3 months interval *Control intervention* Placebo, 8 intra-articular injections, 3 months interval
Outcomes	Outcome data (pain overall, WOMAC) not extractable
Notes	

Rezende 2012

Methods	Randomised controlled trial 2-arm parallel-group design
Participants	104 participants with knee osteoarthritis were randomised
Interventions	*Experimental intervention* 20 mg of hexacetonide triamcinolone plus 6 ml of hylan GF-20, single intra-articular injection *Control intervention* 6 ml of hylan GF-20, single intra-articular injection
Outcomes	Maximum follow-up: 24 weeks Outcome data (VAS, WOMAC, and Lequesne) not extractable
Notes	

Singh 1996

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Outcome data not extractable
Notes	

ICOAP: Intermittent and Constant Osteoarthritis Pain
KOOS: Knee Injury and Osteoarthritis Outcome Score
MRI: magnetic resonance imaging
VAS: visual analogue scale
WOMAC: Western Ontario and McMaster Universities Arthritis Index

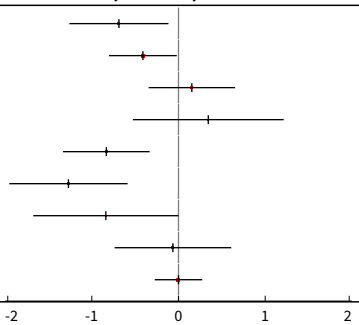
DATA AND ANALYSES

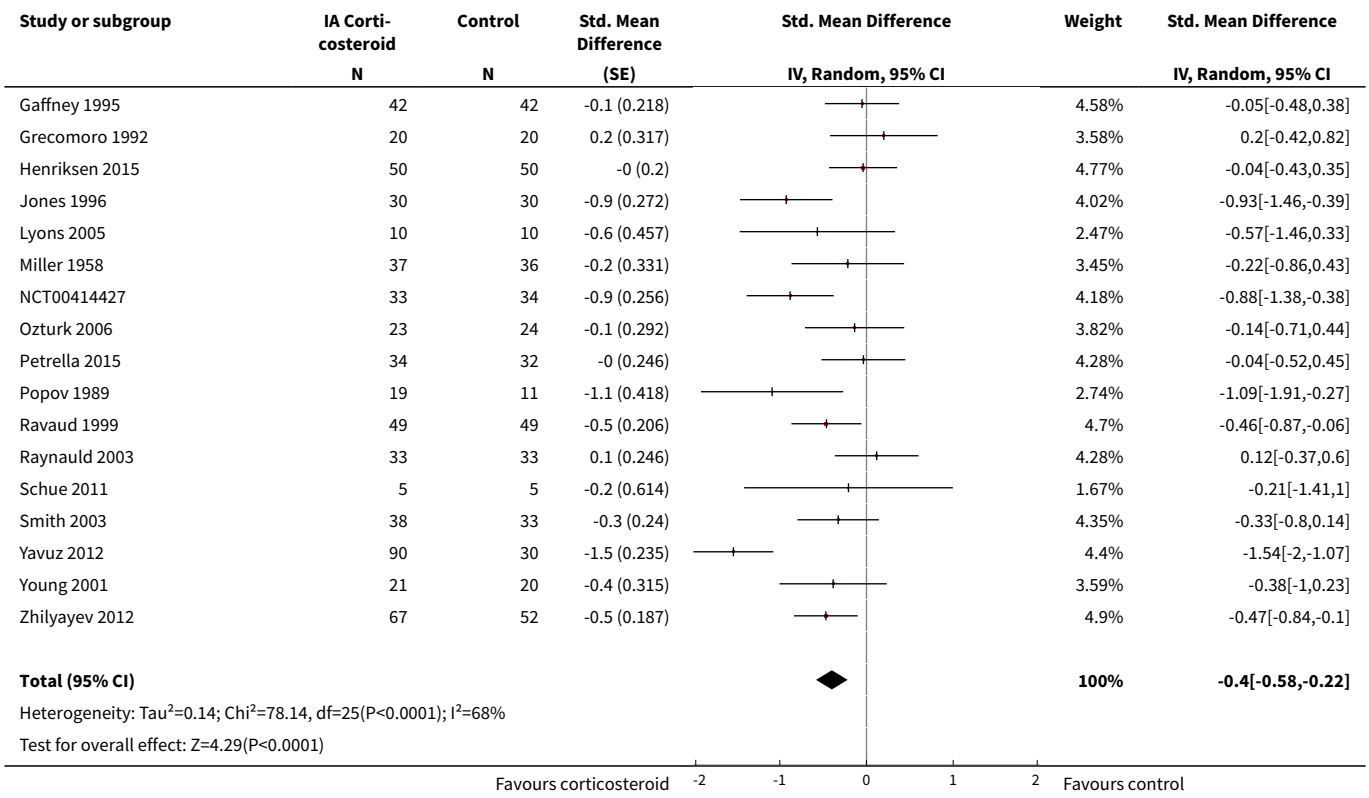
Comparison 1. Pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain - Main	26	1749	Std. Mean Difference (Random, 95% CI)	-0.40 [-0.58, -0.22]
2 Pain - Timepoints	26		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 Pain- 1-2 week	16	1041	Std. Mean Difference (Random, 95% CI)	-0.48 [-0.70, -0.27]
2.2 Pain- 4-6 week	22	1529	Std. Mean Difference (Random, 95% CI)	-0.41 [-0.61, -0.21]
2.3 Pain- 3 months	18	1233	Std. Mean Difference (Random, 95% CI)	-0.22 [-0.44, 0.00]
2.4 Pain- 6 months	7	526	Std. Mean Difference (Random, 95% CI)	-0.07 [-0.25, 0.11]

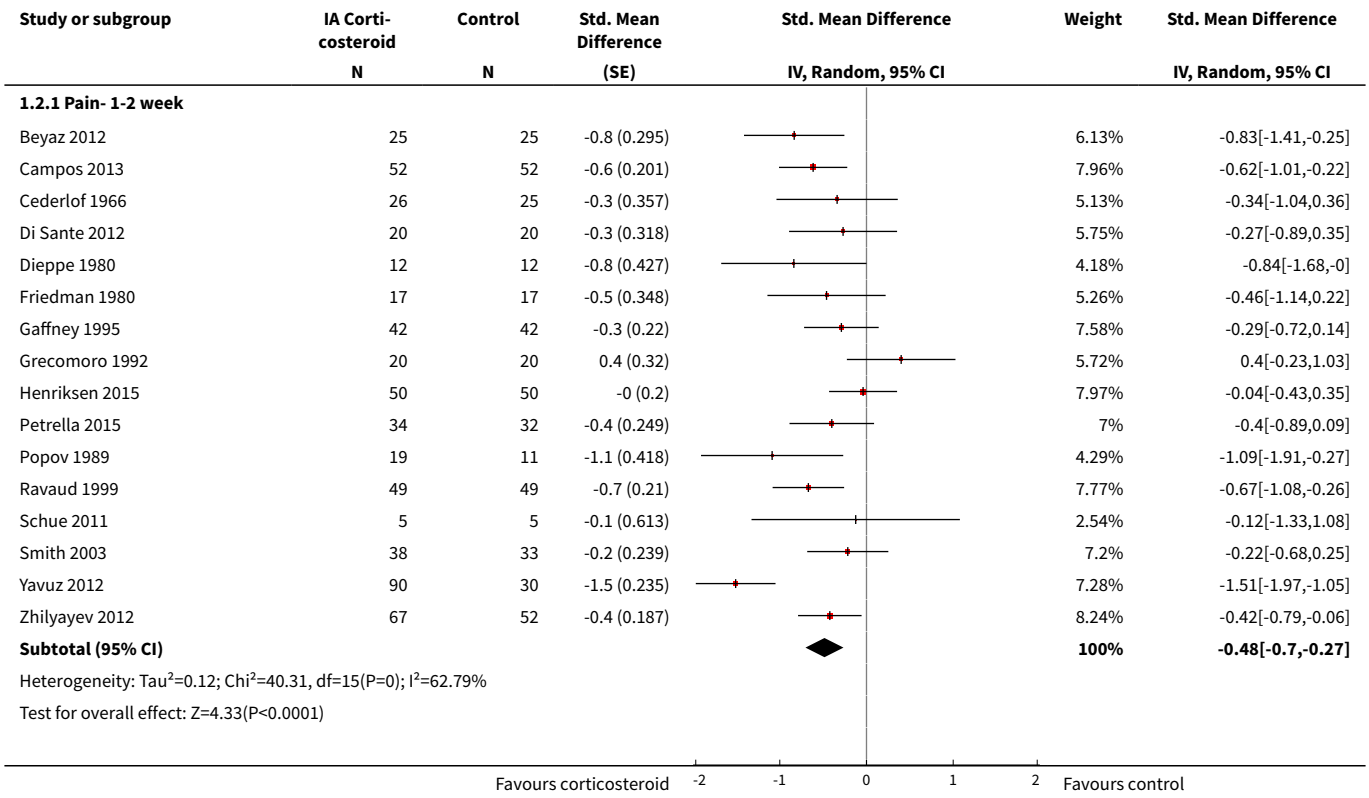
Analysis 1.1. Comparison 1 Pain, Outcome 1 Pain - Main.

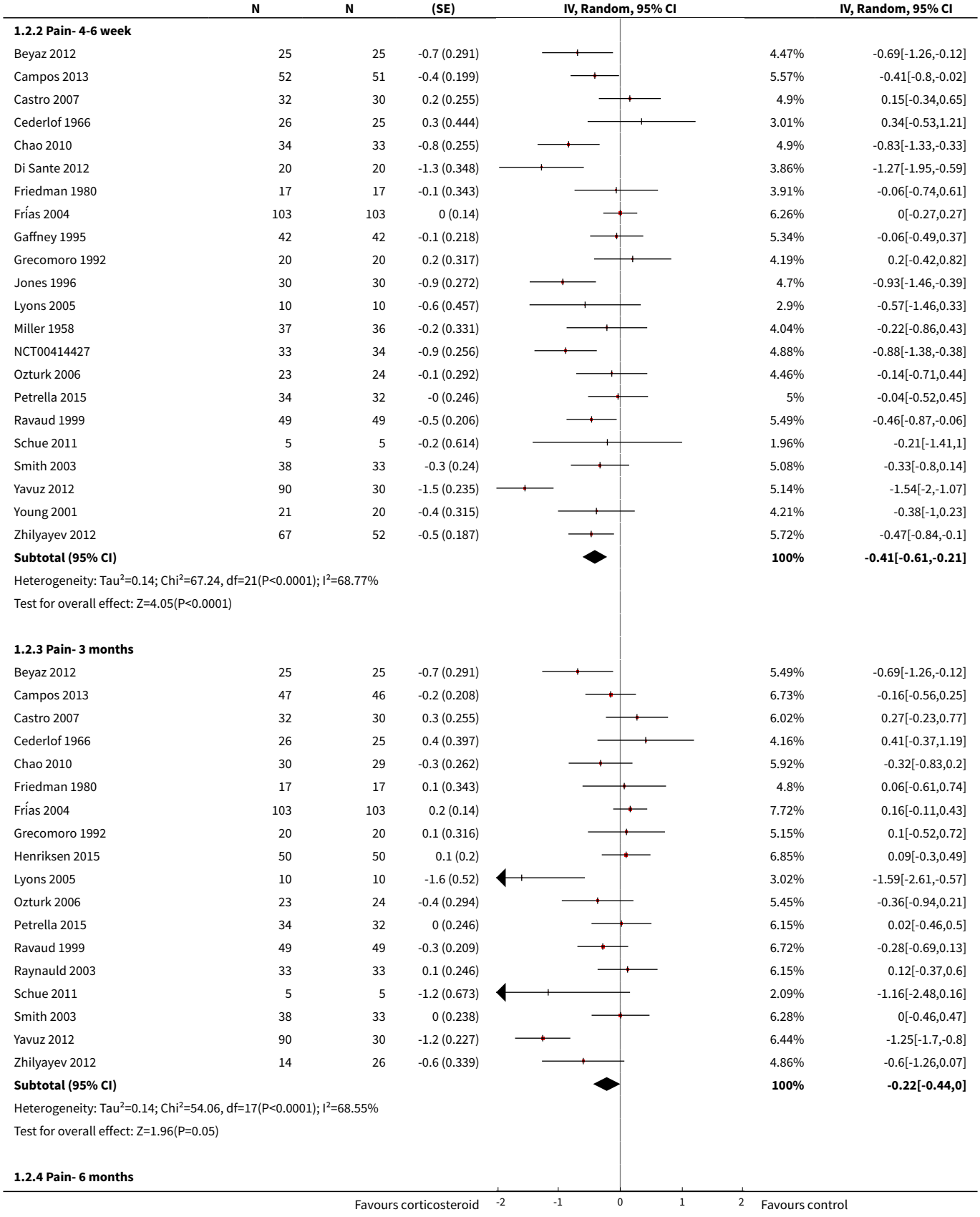
Study or subgroup	IA Corticosteroid N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Beyaz 2012	25	25	-0.7 (0.291)		3.82%	-0.69[-1.26,-0.12]
Campos 2013	52	51	-0.4 (0.199)		4.78%	-0.41[-0.8,-0.02]
Castro 2007	32	30	0.2 (0.255)		4.2%	0.15[-0.34,0.65]
Cederlof 1966	26	25	0.3 (0.444)		2.56%	0.34[-0.53,1.21]
Chao 2010	34	33	-0.8 (0.255)		4.19%	-0.83[-1.33,-0.33]
Di Sante 2012	20	20	-1.3 (0.348)		3.3%	-1.27[-1.95,-0.59]
Dieppe 1980	12	12	-0.8 (0.427)		2.67%	-0.84[-1.68,-0]
Friedman 1980	17	17	-0.1 (0.343)		3.34%	-0.06[-0.74,0.61]
Frías 2004	103	103	0 (0.14)		5.37%	0[-0.27,0.27]



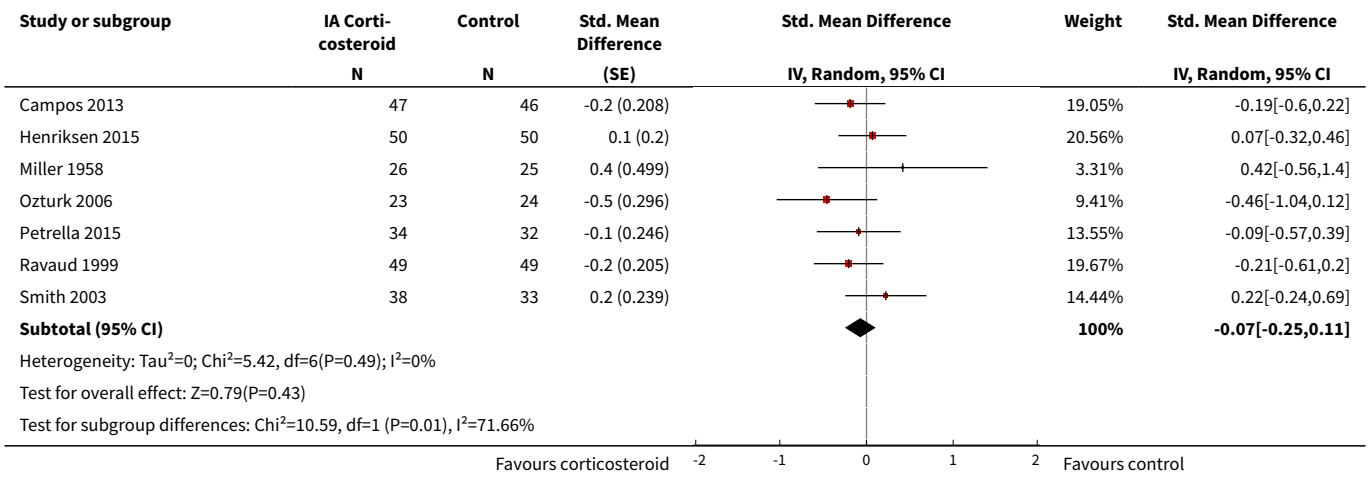


Analysis 1.2. Comparison 1 Pain, Outcome 2 Pain - Timepoints.





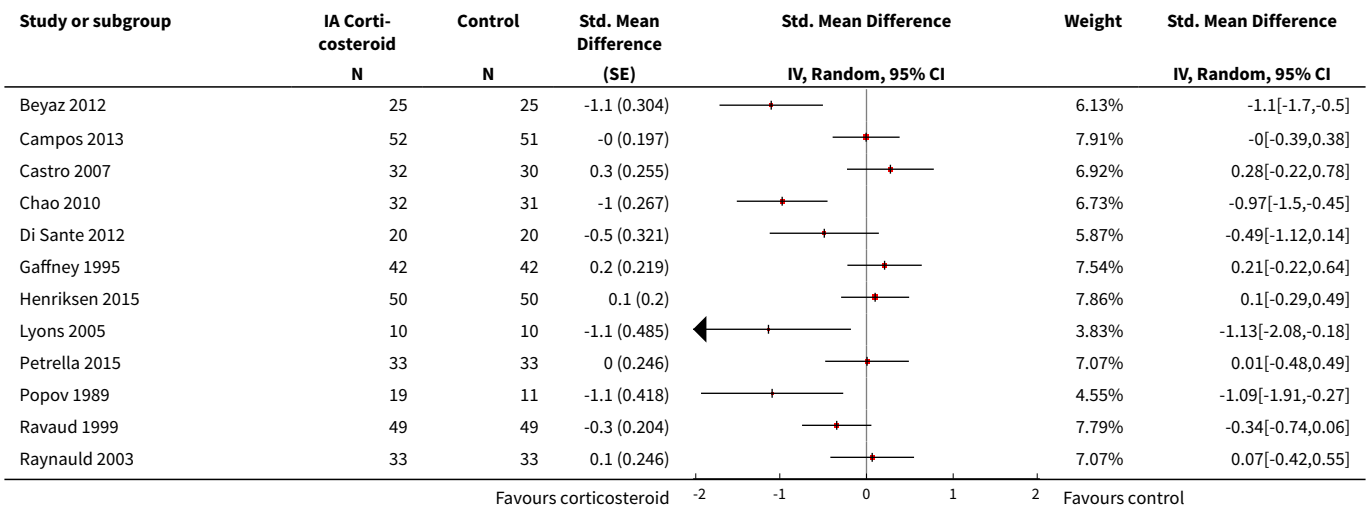
Study or subgroup	IA Corti-costeroid N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.2 Pain- 4-6 week						
Beyaz 2012	25	25	-0.7 (0.291)		4.47%	-0.69[-1.26,-0.12]
Campos 2013	52	51	-0.4 (0.199)		5.57%	-0.41[-0.8,-0.02]
Castro 2007	32	30	0.2 (0.255)		4.9%	0.15[-0.34,0.65]
Cederlof 1966	26	25	0.3 (0.444)		3.01%	0.34[-0.53,1.21]
Chao 2010	34	33	-0.8 (0.255)		4.9%	-0.83[-1.33,-0.33]
Di Sante 2012	20	20	-1.3 (0.348)		3.86%	-1.27[-1.95,-0.59]
Friedman 1980	17	17	-0.1 (0.343)		3.91%	-0.06[-0.74,0.61]
Frías 2004	103	103	0 (0.14)		6.26%	0[-0.27,0.27]
Gaffney 1995	42	42	-0.1 (0.218)		5.34%	-0.06[-0.49,0.37]
Grecomoro 1992	20	20	0.2 (0.317)		4.19%	0.2[-0.42,0.82]
Jones 1996	30	30	-0.9 (0.272)		4.7%	-0.93[-1.46,-0.39]
Lyons 2005	10	10	-0.6 (0.457)		2.9%	-0.57[-1.46,0.33]
Miller 1958	37	36	-0.2 (0.331)		4.04%	-0.22[-0.86,0.43]
NCT00414427	33	34	-0.9 (0.256)		4.88%	-0.88[-1.38,-0.38]
Ozturk 2006	23	24	-0.1 (0.292)		4.46%	-0.14[-0.71,0.44]
Petrella 2015	34	32	-0 (0.246)		5%	-0.04[-0.52,0.45]
Ravaud 1999	49	49	-0.5 (0.206)		5.49%	-0.46[-0.87,-0.06]
Schue 2011	5	5	-0.2 (0.614)		1.96%	-0.21[-1.41,1]
Smith 2003	38	33	-0.3 (0.24)		5.08%	-0.33[-0.8,0.14]
Yavuz 2012	90	30	-1.5 (0.235)		5.14%	-1.54[-2,-1.07]
Young 2001	21	20	-0.4 (0.315)		4.21%	-0.38[-1,0.23]
Zhilyayev 2012	67	52	-0.5 (0.187)		5.72%	-0.47[-0.84,-0.1]
Subtotal (95% CI)					**100%**	**-0.41[-0.61,-0.21]**
Heterogeneity: Tau²=0.14; Chi²=67.24, df=21(P<0.0001); I²=68.77%						
Test for overall effect: Z=4.05(P<0.0001)						
1.2.3 Pain- 3 months						
Beyaz 2012	25	25	-0.7 (0.291)		5.49%	-0.69[-1.26,-0.12]
Campos 2013	47	46	-0.2 (0.208)		6.73%	-0.16[-0.56,0.25]
Castro 2007	32	30	0.3 (0.255)		6.02%	0.27[-0.23,0.77]
Cederlof 1966	26	25	0.4 (0.397)		4.16%	0.41[-0.37,1.19]
Chao 2010	30	29	-0.3 (0.262)		5.92%	-0.32[-0.83,0.2]
Friedman 1980	17	17	0.1 (0.343)		4.8%	0.06[-0.61,0.74]
Frías 2004	103	103	0.2 (0.14)		7.72%	0.16[-0.11,0.43]
Grecomoro 1992	20	20	0.1 (0.316)		5.15%	0.1[-0.52,0.72]
Henriksen 2015	50	50	0.1 (0.2)		6.85%	0.09[-0.3,0.49]
Lyons 2005	10	10	-1.6 (0.52)		3.02%	-1.59[-2.61,-0.57]
Ozturk 2006	23	24	-0.4 (0.294)		5.45%	-0.36[-0.94,0.21]
Petrella 2015	34	32	0 (0.246)		6.15%	0.02[-0.46,0.5]
Ravaud 1999	49	49	-0.3 (0.209)		6.72%	-0.28[-0.69,0.13]
Raynauld 2003	33	33	0.1 (0.246)		6.15%	0.12[-0.37,0.6]
Schue 2011	5	5	-1.2 (0.673)		2.09%	-1.16[-2.48,0.16]
Smith 2003	38	33	0 (0.238)		6.28%	0[-0.46,0.47]
Yavuz 2012	90	30	-1.2 (0.227)		6.44%	-1.25[-1.7,-0.8]
Zhilyayev 2012	14	26	-0.6 (0.339)		4.86%	-0.6[-1.26,0.07]
Subtotal (95% CI)					**100%**	**-0.22[-0.44,0]**
Heterogeneity: Tau²=0.14; Chi²=54.06, df=17(P<0.0001); I²=68.55%						
Test for overall effect: Z=1.96(P=0.05)						
1.2.4 Pain- 6 months						

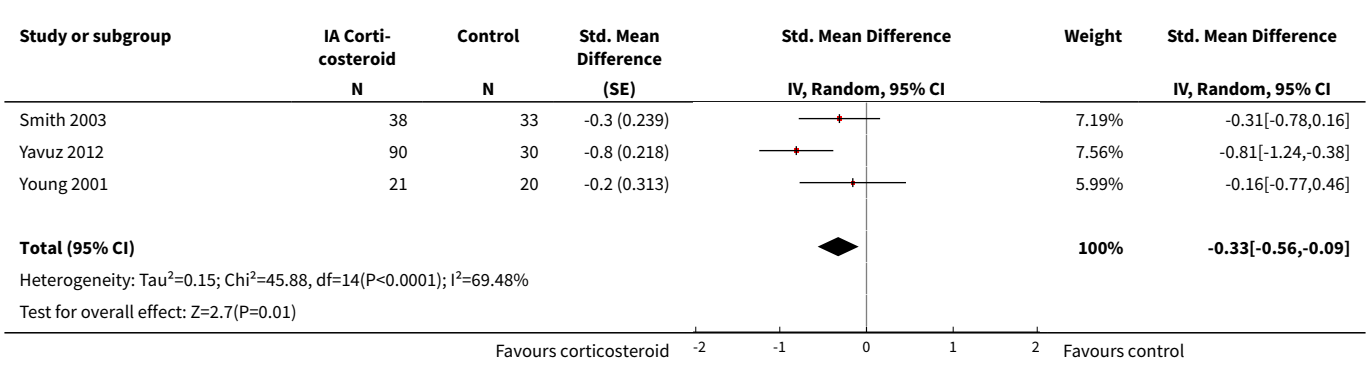


Comparison 2. Function

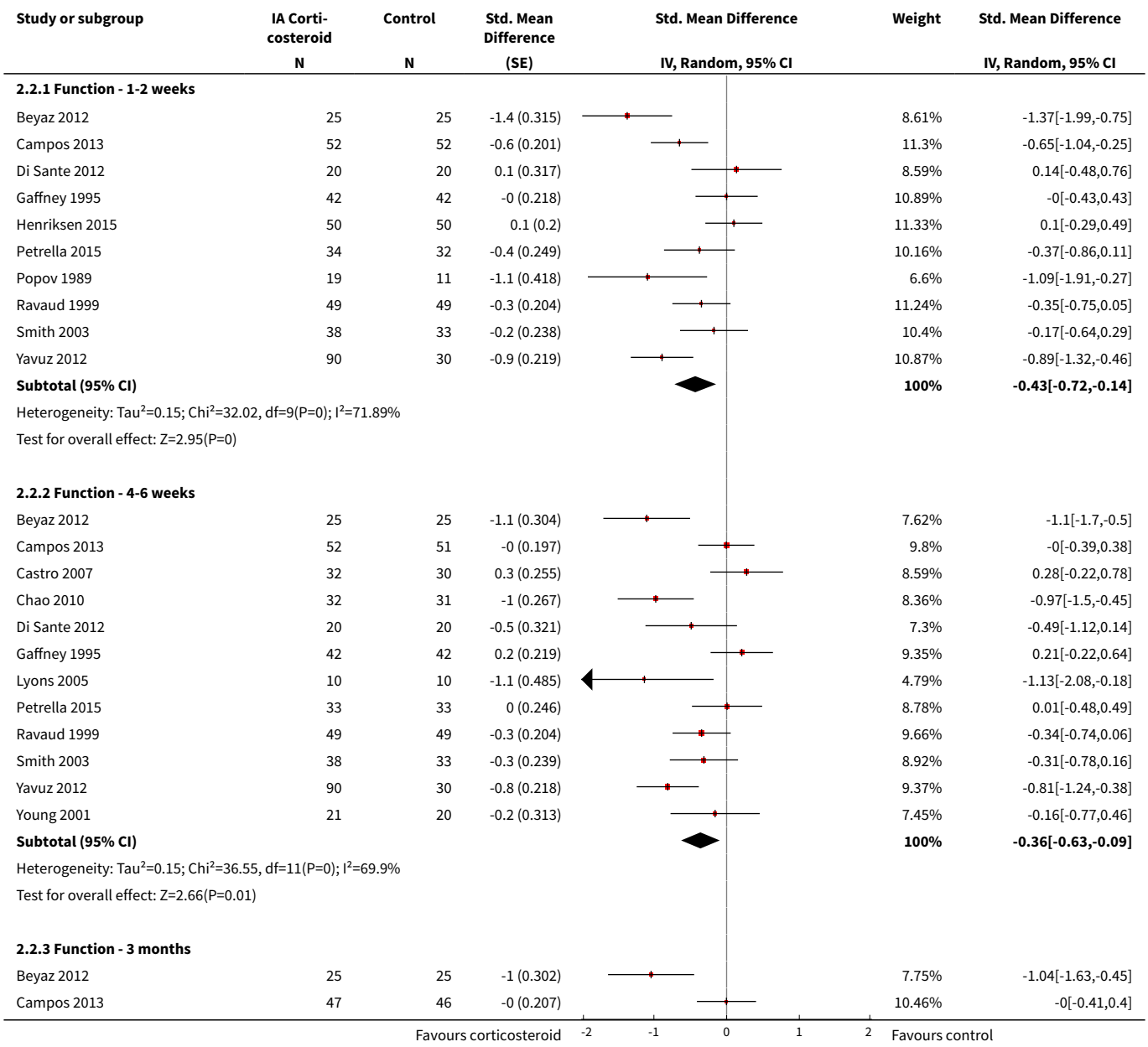
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Function - Main	15	1014	Std. Mean Difference (Random, 95% CI)	-0.33 [-0.56, -0.09]
2 Function - Timepoints	15		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 Function - 1-2 weeks	10	763	Std. Mean Difference (Random, 95% CI)	-0.43 [-0.72, -0.14]
2.2 Function - 4-6 weeks	12	818	Std. Mean Difference (Random, 95% CI)	-0.36 [-0.63, -0.09]
2.3 Function - 3 months	11	800	Std. Mean Difference (Random, 95% CI)	-0.13 [-0.37, 0.10]
2.4 Function - 6 months	4	328	Std. Mean Difference (Random, 95% CI)	0.06 [-0.16, 0.28]

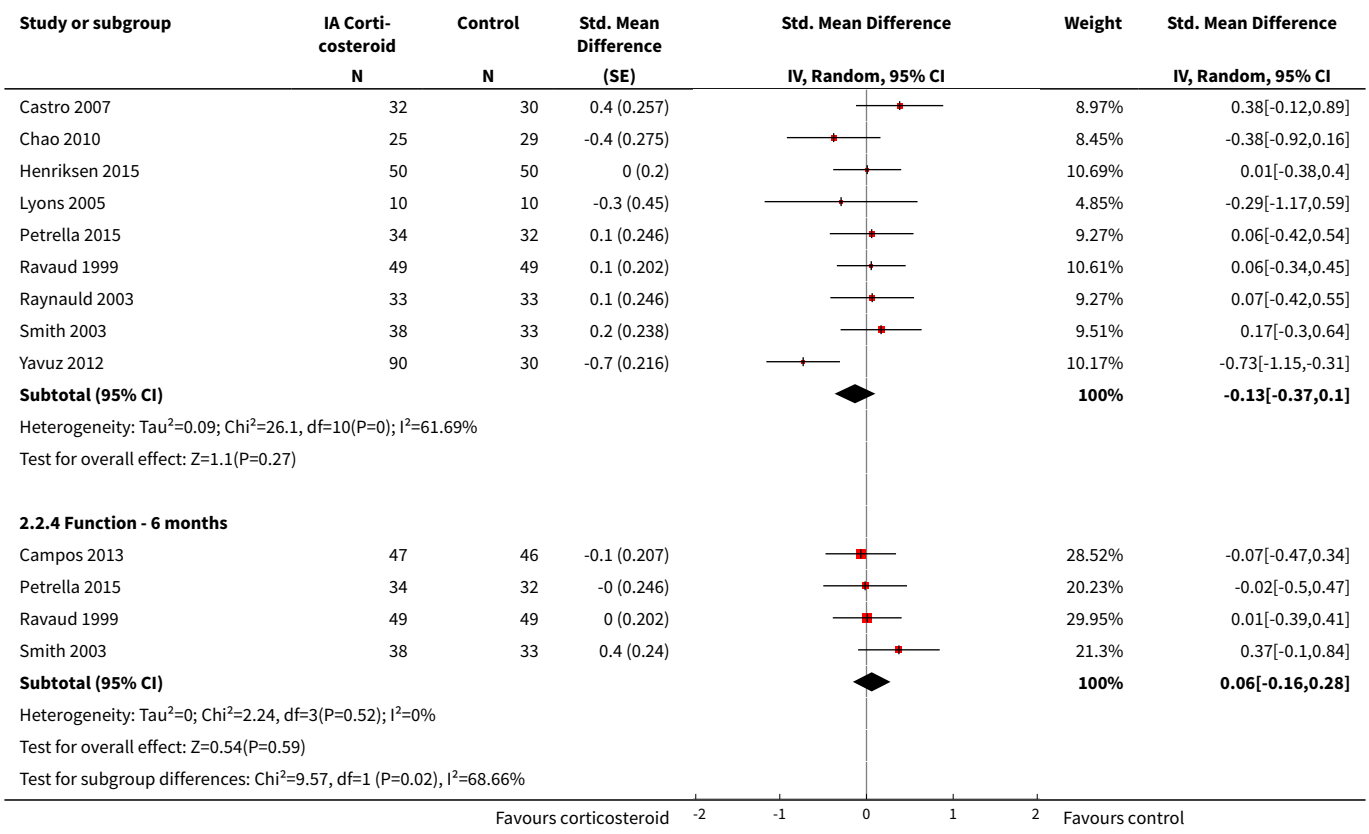
Analysis 2.1. Comparison 2 Function, Outcome 1 Function - Main.





Analysis 2.2. Comparison 2 Function, Outcome 2 Function - Timepoints.

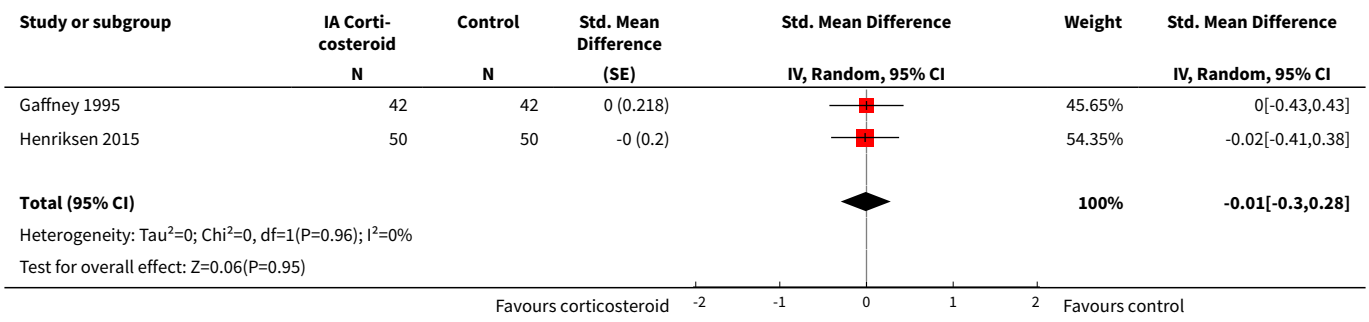




Comparison 3. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life - Main	2	184	Std. Mean Difference (Random, 95% CI)	-0.01 [-0.30, 0.28]

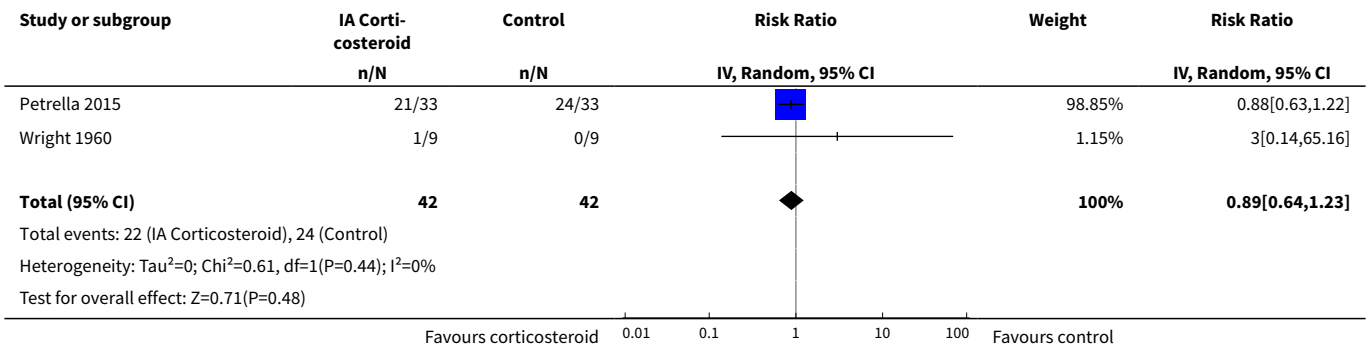
Analysis 3.1. Comparison 3 Quality of life, Outcome 1 Quality of life - Main.



Comparison 4. Number of participants experiencing any adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants experiencing any adverse event - Main	2	84	Risk Ratio (IV, Random, 95% CI)	0.89 [0.64, 1.23]

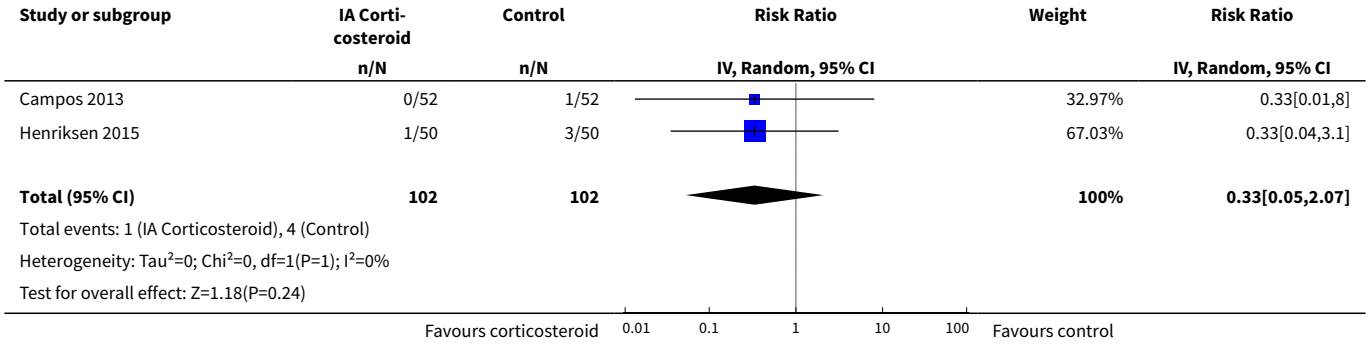
Analysis 4.1. Comparison 4 Number of participants experiencing any adverse event, Outcome 1 Number of participants experiencing any adverse event - Main.



Comparison 5. Number of participants who withdraw because of adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who with draw because of adverse events -Main	2	204	Risk Ratio (IV, Random, 95% CI)	0.33 [0.05, 2.07]

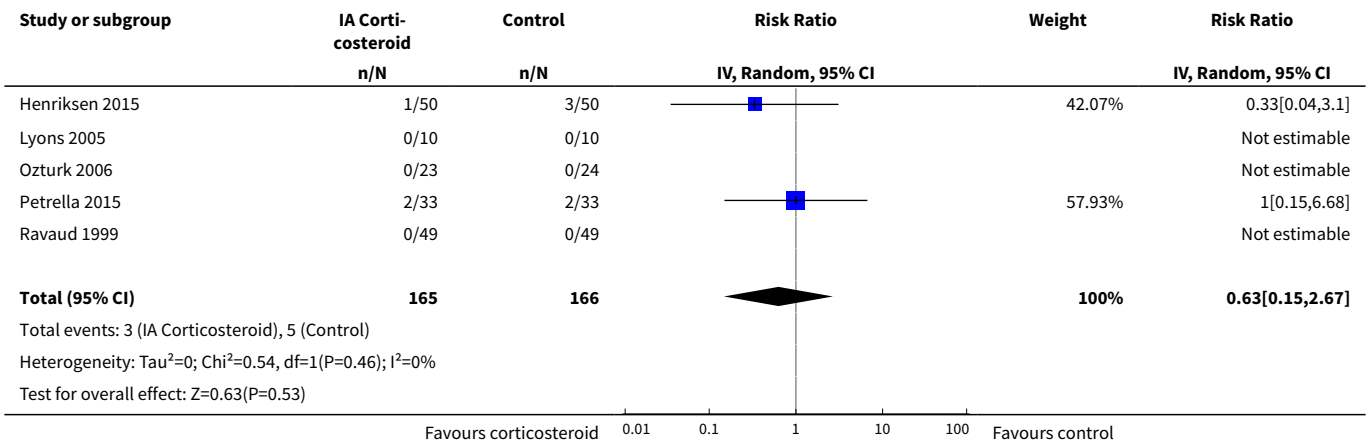
Analysis 5.1. Comparison 5 Number of participants who withdraw because of adverse events, Outcome 1 Number of participants who with draw because of adverse events -Main.



Comparison 6. Number of participants experiencing any serious adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants experiencing any serious adverse event - Main	5	331	Risk Ratio (IV, Random, 95% CI)	0.63 [0.15, 2.67]

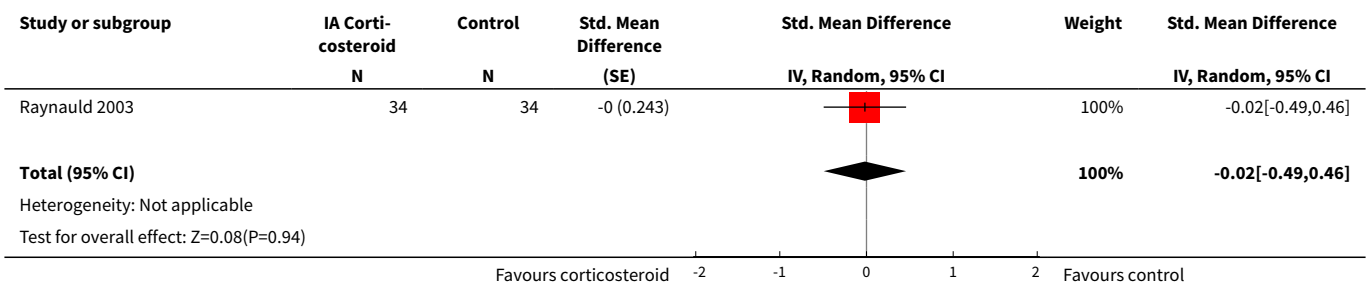
Analysis 6.1. Comparison 6 Number of participants experiencing any serious adverse event, Outcome 1 Number of participants experiencing any serious adverse event - Main.



Comparison 7. Joint space narrowing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint space narrowing - Main	1	68	Std. Mean Difference (Random, 95% CI)	-0.02 [-0.49, 0.46]

Analysis 7.1. Comparison 7 Joint space narrowing, Outcome 1 Joint space narrowing - Main.



ADDITIONAL TABLES

Table 1. Stratified analyses: Pain

Variable	Number of studies	N of participants corticosteroids	N of participants control	Pain intensity SMD (95% CI)	Heterogeneity I^2 (%)	P value*
All trials	26	922	827	-0.40 (-0.58 to -0.22)	68%	
Allocation concealment						0.15
Adequate	2	88	83	-0.16 (-0.46 to 0.14)	0%	
Inadequate or unclear	24	834	744	-0.42 (-0.62 to -0.22)	69%	
Blinding of participants						0.64
Adequate	6	220	218	-0.34 (-0.61 to -0.06)	49%	
Inadequate or unclear	20	702	609	-0.42 (-0.65 to -0.19)	72%	
Blinding of therapists						0.45
Adequate	3	92	92	-0.24 (-0.66 to 0.17)	44%	
Inadequate or unclear	23	830	735	-0.42 (-0.62 to -0.22)	70%	
Intention-to-treat analysis						0.29
Yes	9	236	233	-0.26 (-0.57 to 0.06)	59%	
No or unclear	17	686	594	-0.47 (-0.69 to -0.24)	71%	
Type of control intervention						0.08
Sham injection	19	614	526	-0.50 (-0.72 to -0.28)	65%	
No intervention	7	284	280	-0.18 (-0.47 to 0.11)	63%	
Funding independent of industry						0.80
Yes	11	341	333	-0.37 (-0.55 to -0.18)	26%	
No or unclear	15	581	494	-0.41 (-0.70 to -0.12)	78%	
Trial size						0.05
≥ 50 per trial group	3	205	204	-0.13 (-0.37 to 0.12)	34%	
< 50 per trial group	23	717	623	-0.44 (-0.65 to -0.24)	67%	
Trial size						0.013

Table 1. Stratified analyses: Pain *(Continued)*

≥ 100 per trial group	1	103	103	0.00 (-0.27 to 0.27)	N/A	
< 100 per trial group	25	819	724	-0.42 (-0.61 to -0.23)	66%	
Publication type						0.93
Full journal article	22	785	706	-0.40 (-0.61 to -0.20)	70%	
Other type or unpublished material	4	137	121	-0.38 (-0.84 to -0.08)	65%	
Ultrasound guidance of injections						0.71
Yes	2	70	70	-0.62 (-1.83 to 0.58)	89%	
No or unclear	24	852	757	-0.39 (-0.57 to -0.20)	67%	
Use of local anaesthetic						0.41
Yes	5	172	157	-0.55 (-0.93 to -0.16)	62%	
No or unclear	21	750	670	-0.36 (-0.57 to -0.15)	70%	
Concomitant viscosupplementation						0.08
Yes	4	129	127	-0.16 (-0.42 to 0.09)	4%	
No or unclear	22	793	700	-0.46 (-0.67 to -0.25)	71%	
Concomitant joint lavage						≤ 0.001
Yes	4	197	187	-0.06 (-0.26 to 0.15)	0%	
No or unclear	26	725	640	-0.57 (-0.78 to -0.35)	72%	
Use of crystalline preparation						0.82
Yes	18	623	562	-0.47 (-0.69 to -0.24)	72%	
No or unclear	12	299	265	-0.52 (-0.90 to -0.14)	76%	
Prednisolone equivalence dose						0.53
≥ 50 mg	17	520	470	-0.55 (-0.85 to -0.25)	80%	
< 50 mg	13	402	357	-0.43 (-0.66 to -0.20)	56%	

Number of randomised comparisons are shown in "number of studies" for stratified analyses according to use of lavage as co-intervention, crystalline preparation, prednisolone equivalence. *P value for interaction. N/A: not available.
CI: confidence interval
SMD: standardised mean difference

Table 2. Stratified analyses: Function

Variable	Number of studies	N of participants corticosteroids	N of participants control	Function SMD (95% CI)	Heterogeneity I^2 (%)	P value*
All trials	15	546	468	-0.33 (-0.56 to -0.09)	69%	
Allocation concealment						0.25
Adequate	2	88	83	-0.09 (-0.49 to 0.32)	43%	
Inadequate or unclear	13	458	385	-0.37 (-0.64 to -0.10)	72%	
Blinding of participants						0.97
Adequate	5	201	199	-0.32 (-0.82 to 0.18)	83%	
Inadequate or unclear	10	345	269	-0.33 (-0.59 to -0.07)	58%	
Blinding of therapists						0.78
Adequate	2	75	75	-0.48 (-1.65 to 0.70)	91%	
Inadequate or unclear	13	471	393	-0.31 (-0.55 to -0.06)	66%	
Intention-to-treat analysis						0.49
Yes	5	161	159	-0.21 (-0.59 to 0.17)	62%	
No or unclear	10	385	309	-0.38 (-0.69 to -0.07)	73%	
Type of control intervention						0.031
Sham injection	11	409	334	-0.45 (-0.74 to -0.15)	73%	
No intervention	4	137	134	-0.01 (-0.27 to 0.25)	13%	
Funding independent of industry						0.73
Yes	9	310	302	-0.36 (-0.66 to -0.07)	68%	
No or unclear	6	236	166	-0.27 (-0.71 to 0.16)	76%	
Trial size						0.023
≥ 50 per trial group	2	102	101	0.05 (-0.23 to 0.32)	0%	
< 50 per trial group	13	444	367	-0.40 (-0.67 to -0.13)	70%	
Trial size						N/A
≥ 100 per trial group	0	0	0	N/A	N/A	

Table 2. Stratified analyses: Function *(Continued)*

< 100 per trial group	15	546	468	-0.33 (-0.56 to -0.09)	69%	
Publication type						0.023
Full journal article	14	514	438	-0.37 (-0.61 to -0.13)	68%	
Other type or unpublished material	1	32	30	0.28 (-0.22 to 0.78)	N/A	
Ultrasound guidance of injections						0.49
Yes	2	70	70	-0.14 (-0.70 to 0.43)	58%	
No or unclear	13	476	398	-0.36 (-0.62 to -0.09)	71%	
Use of local anaesthetic						0.34
Yes	4	105	105	-0.60 (-1.25 to 0.05)	78%	
No or unclear	11	441	363	-0.25 (-0.51 to 0.00)	68%	
Concomitant viscosupplementation						0.06
Yes	2	85	84	-0.00 (-0.30 to 0.30)	0%	
No or unclear	13	461	384	-0.39 (-0.66 to -0.12)	72%	
Concomitant joint lavage						0.18
Yes	3	94	84	-0.13 (-0.55 to 0.28)	48%	
No or unclear	16	452	384	-0.46 (-0.71 to -0.21)	70%	
Use of crystalline preparation						0.66
Yes	12	365	319	-0.37 (-0.66 to -0.08)	73%	
No or unclear	7	181	149	-0.47 (-0.83 to -0.11)	61%	
Prednisolone equivalence dose						0.16
≥ 50 mg	12	328	277	-0.52 (-0.83 to -0.20)	74%	
< 50 mg	7	218	191	-0.22 (-0.48 to 0.05)	47%	

Number of randomised comparisons are shown in "number of studies" for stratified analyses according to use of lavage as co-intervention, crystalline preparation, prednisolone equivalence. *P value for interaction. N/A: not available.
CI: confidence interval
SMD: standardised mean difference

APPENDICES

Appendix 1. MEDLINE and PubMed search strategies

MEDLINE*			PubMed†		
Search line	**Search Terms**	**No. citations**	**Search line**	**Search Terms**	**No. citations**
1	*Adrenal Cortex Hormones/ or *17-Hydroxycorticosteroids/ or *11-Hydroxycorticosteroids/ or *Hydroxycorticosteroids/ or *Ketosteroids/ or *17-Ketosteroids/ or *Androstenedione/ or *Prednisolone/ or *Glucocorticoids/ or *Triamcinolone Acetonide/ or *Hydrocortisone/ or *cortisone/	104853	1	((((((osteoarthritis*[tw] OR osteoarthro*[tw] OR gonarthriti*[tw] OR gonarthro*[tw] OR coxarthriti*[tw] OR coxarthro*[tw] OR arthros*[tw] OR arthrot*[tw] OR ((knee*[tw] OR hip[tw] OR hips[tw] OR joint*[tw]) near/3 (pain*[tw] OR ache[tw] OR aches[tw] OR aching[tw] OR achy[tw] OR discomfort*[tw])) OR ((knee*[tw] OR hip[tw] OR hips[tw] OR joint*[tw]) near/3 stiff*[tw]))))) AND ((adrenal cortex hormone*[tw] OR adrenal cortical hormone*[tw] OR adrenal steroid*[tw] OR adrenocortical hormone*[tw] OR adrenocortical steroid*[tw] OR adrenocorticalsteroid*[tw] OR adrenocorticosteroid*[tw] OR cortical steroid*[tw] OR cortico-steroid*[tw] OR corticoid*[tw] OR corticosteroid*[tw] OR dermocortico-steroid*[tw] OR dermocorticosteroid*[tw] OR glucocortic*[tw] OR hydroxycorticosteroid*[tw] OR ketosteroid*[tw] OR androstenedion*[tw] OR steroid[tw] OR triamcinolone hexacetonide[tw] OR hydrocortison*[tw] OR prednisolone[tw] OR Prednison*[tw] OR cortison*[tw] OR Pregnadiene*[tw])))) AND ((intraartic*[tw] OR intra-artic*[tw] OR inject*[tw] OR infiltration*[tw] OR infiltrating[tw])))) AND (((clinical[Title/Abstract] AND trial[Title/Abstract]) OR “clinical trial”[tw] OR “clinical trials”[tw] OR random*[tw] OR "therapeutic use"[tw] OR placebo[tw] OR sham[tw]))) AND publisher[sb]	
2	(adrenal cortex hormone* or adrenal cortical hormone* or adrenal steroid* or adrenocortical hormone* or adrenocortical steroid* or adrenocorticalsteroid* or adrenocorticosteroid* or cortical steroid* or cortico-steroid* or corticoid* or corticosteroid* or dermocortico-steroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or steroid or triamcinolone hexacetonide or hydrocortison* or prednisolone or Prednison* or cortison* or Pregnadiene*).mp.	429888			
3	or/1-2	430785			
4	(intraartic* or intra-artic* or inject* or infiltration* or infiltrating).mp.	831275			
5	exp osteoarthritis/	44274			
6	(osteoarthriti$ or osteoarthro$ or gonarthriti$ or gonarthro$ or coxarthriti$ or coxarthro $).ti,ab,sh.	62668			
7	(arthros$ or arthrot$).ti,ab.	26671			
8	((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.	20156			
9	((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	2914			
10	or/5-9	101715			

(Continued)

11	(randomized controlled trial or controlled clinical trial).pt.	465958			
12	(randomized or placebo or randomly or groups or trial).ab.	1916245			
13	drug therapy.fs.	1728855			
14	or/11-13	3430383			
15	random*.ti,ab.	739136			
16	or/14-15	3575985			
17	and/3-4,10,16	766			
18	exp animals/ not humans.sh.	3974624			
19	17 not 18	719			
20	remove duplicates from 19	**713**			**6**

* Search performed at 02nd of February 2015, using the following database in OvidSP: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

† Top-up search in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) at 03rd Februari 2015, to retrieve citations not yet indexed in OvidSP MEDLINE databases

Appendix 2. EMBASE and CENTRAL search strategies

EMBASE*			**CENTRAL†**		
Search line	**Search Terms**	**No. citations**	**Search line**	**Search Terms**	**No. citations**
1	*Adrenal Cortex Hormones/ or *17-Hydroxycorticosteroids/ or *11-Hydroxycorticosteroids/ or *Hydroxycorticosteroids/ or *Ketosteroids/ or *17-Ketosteroids/ or *Androstenedione/ or *Prednisolone/ or *Glucocorticoids/ or *Triamcinolone Acetonide/ or *Hydrocortisone/ or *cortisone/	191907	#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	11438
			#2	MeSH descriptor: [Prednisolone] explode all trees	3470
			#3	MeSH descriptor: [Hydrocortisone] explode all trees	4565
2	(adrenal cortex hormone* or adrenal cortical hormone* or adrenal steroid* or adrenocortical hormone* or adrenocortical steroid* or adrenocorticalsteroid* or adrenocorticos-	871195	#4	MeSH descriptor: [Triamcinolone Acetonide] explode all trees	603

(Continued)

	teroid* or cortical steroid* or cortico-steroid* or corticoid* or corticosteroid* or dermo-cortico-steroid* or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or steroid or triamcinolone hexacetonide or hydrocortison* or prednisolone or Prednison* or cortison* or Pregnadiene*).mp.		#5	MeSH descriptor: [Ketosteroids] explode all trees	962
			#6	"adrenal cortex hormone*" or "adrenal cortical hormone*" or "adrenal steroid*" or "adrenocortical hormone*" or "adrenocortical steroid*" or "adrenocorticalsteroid*" or "adrenocorticosteroid*" or "cortical steroid*" or "cortico-steroid*" or corticoid* or corticosteroid* or "dermocortico-steroid*" or dermocorticosteroid* or glucocortic* or hydroxycorticosteroid* or ketosteroid* or androstenedion* or steroid or "triamcinolone hexacetonide" or hydrocortison* or prednisolone or Prednison* or cortison* or Pregnadiene*	33629
3	or/1,2	874556			
4	(intraartic* or intra-artic* or inject* or infiltration* or infiltrating).mp.	1069778			
5	exp osteoarthritis/	92440	#7	#1 or #2 or #3 or #4 or #5 or #6	35680
6	(osteoarthriti$ or osteoarthro$ or gonarthriti$ or gonarthro$ or coxarthriti$ or coxarthro$).ti,ab,sh.	96428	#8	intraartic* or intra-artic* or inject* or infiltration* or infiltrating	52930
7	(arthros$ or arthrot$).ti,ab.	36551	#9	MeSH descriptor: [Osteoarthritis] explode all trees	3605
8	((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.	29955	#10	(osteoarthritis* or osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or arthros* or arthrot* or ((knee* or hip* or joint*) near/3 (pain* or ach* or discomfort*)) or ((knee* or hip* or joint*) near/3 stiff*))	12050
9	((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.	4364	#11	#9 or #10	12050
10	or/5-9	160749	#12	#7 and #8 and #11	481

(Continued)

11	exp clinical trial/ or exp evaluation studies/	1017697	#13	#7 and #8 and #11 [in trials]	**264**
12	(clin$ adj25 trial$).ti,ab. or ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. or (placebo$ or random$ or control$ or prospectiv$ or volunteer$).ti,ab.	4813156			
13	(randomized controlled trial or randomization or double blind procedure or single blind procedure or methodology or follow up or prospective study or comparative study or placebo).sh.	3749360			
14	or/11-13	7670295			
15	and/3-4,10,14	1364			
16	animals/ not humans/	1206540			
17	15 not 16	1356			
18	remove duplicates from 17	**1341**			

* Search performed at 03rd of February 2015, using the following database in OvidSP: Embase Weekly Alerts 2014/07/28-Present, Embase Classic+Embase 1947 to Present

† Search performed at 03rd of February 2015, using the Cochrane Library of the publisher Wiley at http://onlinelibrary.wiley.com/cochranelibrary/search.

WHAT'S NEW

Date	Event	Description
2 November 2015	Amended	Typo corrected.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 2, 2005

Date	Event	Description
2 September 2015	New citation required and conclusions have changed	The review has been updated since last version of 2006.

CONTRIBUTIONS OF AUTHORS

Protocol completion: Jüni, Rutjes, Reichenbach, da Costa.
Acquisition of data: Hari, Rutjes, Fischer, Silletta, da Costa.
Analysis and interpretation of data: Jüni, Hari, Reichenbach, da Costa.
Manuscript preparation: Jüni, Hari, da Costa.
Statistical analysis: Jüni, da Costa.

DECLARATIONS OF INTEREST

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies

In the previous version of this Cochrane Review, only RCTs were eligible for inclusion, while in the present review update both RCTs and quasi-RCTs were eligible.

Types of interventions

In the previous review version, control interventions were both sham intra-articular corticosteroid and active interventions (joint lavage, intra-articular hyaluronan/hylan, and other intra-articular corticosteroids). In the present review update, the prespecified control interventions were sham intra-articular corticosteroid and no intervention.

Types of outcome measures

In the previous review version there were eight outcomes: pain, physical function, patient global assessment, joint imaging, adverse reaction caused by procedure, adverse reaction caused by corticosteroid, adverse reaction caused by toxicity-related withdrawals, total number of withdrawals and dropouts. In the review update, there were two prespecified primary outcomes and six prespecified secondary outcomes. Primary outcomes were pain and physical function, and secondary outcomes were quality of life, joint imaging, and the number of participants who experienced any adverse event, withdrew because of adverse events, and experienced any serious adverse events.

Search methods for identification of studies

In the previous review version, the following four databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (including PreMEDLINE), EMBASE, and Current Contents. The electronic searches were supplemented by handsearches of bibliographic references and abstracts published in conference proceedings or in special issues of specialised journals, and industry representatives were contacted to request additional studies of their product that could meet eligibility criteria. In the present review update, we searched the following three databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid and PubMed platforms, and EMBASE. The electronic searches were supplemented by handsearches of bibliographic references, abstracts published in conference proceedings, and search of clinical trial registers to identify ongoing or recently concluded trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Arthralgia [*drug therapy] [etiology]; Hyaluronic Acid [administration & dosage] [adverse effects] [analogs & derivatives] [therapeutic use]; Injections, Intra-Articular; Osteoarthritis, Knee [*drug therapy] [therapy]; Pain Measurement; Randomized Controlled Trials as Topic; Therapeutic Irrigation [methods]

MeSH check words

Humans