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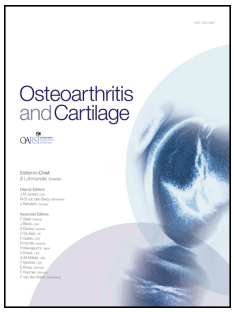

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The efficacy of intra-articular steroids in hip osteoarthritis: A systematic review

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Running head: Intra-articular steroids in hip OA

ABSTRACT

OBJECTIVE: International guidelines recommend intra-articular steroid injections (IASI) in the management of hip osteoarthritis (OA), though these recommendations are extrapolated primarily from studies of knee OA. The aim of this systematic review was to assess the efficacy of IASI on pain in hip OA.

METHODS: MEDLINE, EMBASE, AMED, CINAHL Plus, Web of Science and the Cochrane Central Register of Controlled Trials were searched to May 2015. RCTs assessing the efficacy of hip IASI on pain were included. Pre-specified data was extracted using a standardised form. Quality was assessed using the Jadad score.

RESULTS Five trials met the inclusion criteria. All had a small number of participants (≤101). All studies reported some reduction in pain at 3-4 weeks post-injection compared to control. Based on data from individual trials the treatment effect size was large at 1 week post-injection but declined thereafter. A significant (moderate effect size) reduction in pain was reported in 2 trials up to 8 weeks following IASI. Pooled results of 2 trials (N=90) showed an increased likelihood of meeting the OMERACT-OARSI response criteria at 8 weeks post-IASI, odds ratio 7.8 (95% CI 2.7-22.8). The number needed to treat to achieve one OMERACT-OARSI responder at 8 weeks post-injection was 2.4 (95% CI 1.7-4.2). Hip IASI appear to be generally well tolerated.

CONCLUSIONS: Hip IASI may be efficacious in short term pain reduction in those with hip OA though the quality of the evidence was relatively poor. Further large, methodologically rigorous trials are required to verify whether intra-articular corticosteroids are beneficial and for how long.

KEYWORDS: Hip, osteoarthritis, intra-articular injection, steroids, pain, function, response, systematic review

INTRODUCTION

To date there are no effective therapies which reduce disease progression in hip OA and management is primarily focused on optimum pain control and maintaining function. There are, however, limitations with current analgesic therapies. Oral analgesic therapy is restricted by duration, degree of efficacy and considerable associated toxicities.[1] Non-steroidal anti-inflammatory drugs are associated with significant morbidity and mortality,[2] exacerbated by the co-morbidities that are frequent in a typical OA population, whilst other analgesic medications, for example codeine, can cause nausea, constipation and drowsiness.[3]

Intra-articular steroid therapy offers a potentially useful therapy as it is directly targeted at the affected joint with few systemic effects. Current guidelines produced by European League Against Rheumatism (EULAR),[4] the American College of Rheumatology (ACR)[5] and Osteoarthritis Research Society International (OARSI)[6] also recommend their use in the management of hip OA. However, as acknowledged by the ACR expert panel 'few trials have been performed in patients with symptomatic hip OA,' and their recommendations are based on their assessment that 'patients with hip OA should be treated in a similar fashion to those with knee OA.'[5] A previous narrative review in 2008 concluded that, although there was a lack of evidence of efficacy and safety of IASI in hip OA, there was some evidence of short-term pain relief.[7] To date there have been no systematic reviews of the impact of IASI in the management of hip OA.

The objective of this systematic review was to assess the efficacy of IASI in reducing pain in patients with hip OA. A secondary objective was to assess the effects of hip IASI on function and also evaluate safety.

METHODS

Literature search

MEDLINE, EMBASE, AMED, CINAHL Plus, Web of Science and the Cochrane Central Register of Controlled Trials were searched from inception to May 2015. No restrictions on language or date were applied. Search terms included synonyms of *hip osteoarthritis, intra-articular injection, injection and steroids* and common steroids used in intra-articular injections (methylprednisolone, triamcinolone and betamethasone) and associated brand names. Each database was searched individually with the search strategy optimised based on indexing method. Search terms were searched for both as free text and using terms indexed in each databases thesaurus (i.e. MeSH) where applicable. Full details of the MEDLINE search strategy appear in the supplementary data, available at *Rheumatology* online. To maximise the sensitivity of the search strategy no randomised controlled trial (RCT) or language filter was applied. Reference lists of relevant articles, reviews and clinical guidelines were also hand searched. To identify relevant unpublished trials the WHO Trial Search Portal and UK Clinical Trials Gateway were also searched. Eligibility assessment of trials for inclusion in the review was performed unblinded by 1 reviewer (P.S.M.) using a standardised form.

Study selection

This review included RCTs that assessed the use of hip IASI, using any steroid preparation, in patients with painful hip OA. The diagnosis of hip OA must have been based on the presence of hip pain and radiological evidence of OA. All trials must have included an intervention group which received a hip IASI and a control group who received a placebo (sham injection, normal saline or local anaesthetic intra-articular injection). Trials comparing IASI with another active treatment without a control group were excluded.

Outcome measures

The *a priori* outcome of interest was self-reported pain. Data was extracted for all reported pain measures and for the secondary outcome of function. Previous reports suggest that IASI in the knee have a significant, but relatively short lived effect on pain and may also have transient effects on function[8] and therefore we extracted pain and function outcome data at all reported time points.

Quality Assessment

The quality of included trials was independently assessed by reviewers (P.S.M and N.M.) using the scoring system suggested by Jadad *et al*,[9] a widely used and validated quality assessment tool for RCTs which includes assessment of blinding, randomisation and reporting of withdrawals and drop outs.[9, 10] In the event of disagreement the reviewers discussed their assessment to reach a consensus.

Data Extraction

Two authors (P.S.M and N.M.) independently extracted data from all studies utilising a standardised proforma.

Quantitative Synthesis

A quantitative synthesis of the OMERACT-OARSI response status at 8 weeks post-injection incorporating the results of 2 studies was performed. Analysis was undertaken in Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen) utilising a Mantel-Haenszel model. We used a fixed effects approach as there was little heterogeneity in the 2 studies.

We also performed a further analysis, which considered the pain outcomes reported in the included studies. We took data from the highest 'rated' pain outcome available from each of the included trials, according to the hierarchy described by Jüni et al.[1] at the longest available reported follow-up visit. Given the likelihood of high heterogeneity between trials with different follow-up lengths, and pain outcomes, we opted to use a random-effects Mantel-Haenszel model for this analysis, since it is more robust to heterogeneity in effects. Standardised mean differences were constructed, comparing the mean change in each pain outcome, between the active and control groups featured in each trial. Where within-person standard deviations in pain outcome were not reported, we contacted authors to obtain the unreported data. Where a response was not available, we imputed the mean difference standard deviations ($SD_{(baseline\text{-}follow\text{-}up)}$) by combining the standard deviations reported at baseline and follow up, with an estimated correlation between baseline and follow up visits of 0.5, and sensitivity analyses using correlations of 0.25 and 0.75, as per Cochrane Collaboration recommendations, [11] using the following formula:

$$SD_{(baseline\text{-}follow\text{-}up)} = \sqrt{SD^2_{baseline} + SD^2_{follow\text{-}up} - (2 \times Cor_{(baseline,follow\text{-}up)}) \times SD_{baseline} \times SD_{follow\text{-}up}}$$

RESULTS

Search results

The search of literature databases identified 488 records potentially relevant to the study question (Figure 1). After removal of duplicates, 362 records remained and screening of the record title or abstract allowed exclusion of 324. For the remaining 36 records the full text article was read with 5 studies meeting the inclusion criteria.[12-16] The reasons for exclusion included lack of randomisation,[17] no placebo control group,[18] clinical guideline only,[5-7] review article,[19-32] injection methods article or review,[33-36] trial protocol only[37] and others.[38-45]

A search of trial registries identified one unpublished trial (clinical trials registration number NCT01079455) which was potentially relevant to this review. A published protocol for the trial was identified[37] and if performed per protocol would have met the review inclusion criteria. However, no published results were identified and the corresponding author did not respond to a request for further information.

Characteristics of included studies

A summary of the characteristics of included trials is shown in Table 1. Across all 5 included trials 346 participants were randomised and 134 received a hip IASI. All trials were of a parallel design. The hip OA populations studied included those awaiting or eligible for a total hip arthroplasty (THA),[13,14,16] those refractory to simple analgesia [12] or any person meeting the ACR criteria for OA of the hip.[15] Three different steroid preparations (methylprednsiolone acetate[13,15] triamcinolone acetonide[16] and triamcinolone hexacetonide[12] were utilised and all studies used a different dose as shown in Table 1. One study did not report which triamcinolone salt was utilised.[14] All intra-articular injections were performed under image guidance either by ultrasound[13,15] or fluoroscopy.[12,14.16]

All studies had patient-reported pain as a primary outcome and 4 also included some assessment of function.[12,13,15,16]. A variety of different outcome measures were employed to assess pain including: numerical rating scale (NRS) of pain in general,[14] NRS worst pain,[13] visual analogue scale (VAS) of pain on weight bearing/walking and at rest,[15,16] and the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) pain subscale.[12] Objective functional assessment included passive hip range of motion (ROM) [12.16]and subjective functional assessments: modified Katz ADL index,[16] SF-36 physical and social function score[12] and subjective algo-functional assessments (Lequesne index[15] and WOMAC global score[13,15]). Additional outcome measures included the Osteoarthritis Research Society International and Outcome measures in Rheumatology Clinical Trials (OARSI/OMERACT) response criteria[13,16] and patient global assessment.[13,15] All studies reported follow up durations of at least 8 weeks.

Quality Assessment

The quality of included trials was assessed using the Jadad scoring system and results are shown in Table 2. All studies scored 3 or more indicating high quality study design. Four studies were described as double blind [12,14-16] and one as single blind.[13] The inclusion of a single blind trial is unlikely to have introduced significant bias as the patients were blinded to treatment allocation and the trial only considered self-reported outcome measures.[13]

Flanagan *et al* 1988,[14] prioritised participants for THA if they reported being worse at any follow up time point after intra-articular injection and were also censored from further participation in the trial. As the participants were aware of this from the outset there may have been an incentive to report being worse after the injection, however the study was double blind and therefore it was unlikely to have significantly affected the between group comparison. In this study after 1 month follow up the effect on pain is reported at different time points for the IASI group and the

bupivacaine control group rendering it impossible to compare results between groups. The results beyond 1 month have therefore not been considered in this review.

In Kullenberg *et* al 2004,[16] a double blind trial, the entire control group (n=40) withdrew after the 3 weeks follow up which the authors report was due to inefficacy and thus there was no control group at 12 weeks, the primary end point. Only the results up to the 3 weeks post-injection have been included in the review.

Effect on Pain

A summary of the effect on pain for individual trials is shown in Figure 2. All trials reported some reduction in pain 3-4 weeks post hip IASI compared to controls across a diverse range of pain outcome measures. Outcome beyond 4 weeks follow up was assessed in 3 trials.[12,13,15] Two trials included follow up at 8 weeks post-injection, and both reported clinically significant reductions in pain in the hip IASI group, compared to control, in either NRS of worst pain and/or WOMAC pain subscale.[12,13] At 8 weeks, across both trials, 29 of the 50 participants who received a hip IASI met the OMERACT-OARSI response criteria compared to only 6 out of 40 who received a control injection. As shown, Figure 3, a fixed-effects Mantel-Haenszel estimate of this effect gives an odds ratio of 7.8 (95% CI 2.7-22.4), favouring IASI. The risk difference for this odds ratio was 0.41 (95% CI 0.24-0.58) giving a number needed to treat to achieve 1 OMERACT-OARSI responder at 8 weeks post-injection of 2.4 (95% CI 1.7-4.2).

Only one trial, Qvistgaard *et al*[15] reported the results beyond 8 weeks. They reported a statistically significant reduction in pain in walking in the IASI group averaged across all follow up time points (2, 4 and 12 weeks), with an overall moderate effect size (standardised mean difference, SMD) of 0.6 (95% CI: 0.1-1.1). However, the difference between steroid and placebo groups in pain on walking was only statistically significant up to 4 weeks post injection, ($P_{2\ weeks}$=0.006, P_4

$_{weeks}$=0.006, $P_{12\ weeks}$=0.58). In contrast to Kullenberg *et al*[16] no significant reduction in pain at rest was reported at 3 weeks.

The magnitude of pain reduction following hip IASI appears to be initially large but deceases over time. Atchia *et al*[13] reported an SMD of 1.5 and 1.9 for NRS worst pain and WOMAC pain subscale respectively 1 week post-injection. However by 4 weeks this had decreased to 1.0 and 1.1 and at 8 weeks post-injection to 0.5 and 0.6 for NRS worst pain and WOMAC pain subscale respectively. Although the results reported by Lambert *et al*[12] suggest a less marked decrease in efficacy between 4 and 8 weeks, in keeping with all trials included in this review, insufficient data was available in the original publication to allow calculation of treatment effect size. The corresponding authors for the three published papers in the last 10 years[13,14,16] were contacted to request additional information, or anonymised raw patient data, however, no additional information was obtained. Given the limited degree of available data, it was not possible to combine trial data in a formal meta-analysis (other than the limited fixed-effects odds-ratio estimate of OMERACT-OARSI responders, using the 8 weeks time point from two of the included studies).

Figure 3 depicts a forest plot summarising the overall effect for the three trials which reported data on change in pain outcomes measured on a continuous scale. Overall, the observed degree of heterogeneity in effects in these trials was very high (I^2 = 97%, p<0.001). The pooled overall SMD from these three trials was generally in favour of hip IASI, however this difference was not deemed statistically significant at the 0.05 level (SMD = -1.90; 95% CI -4.07 to 0.26; p = 0.08). Data from Atchia *et al*[13] did not report the required information to allow inclusion in this analysis, and imputed standard deviations were generated for the Lambert and Kullenberg *et al* trials[12,16[. Kullenberg *et al* reported data at follow up at both 3 weeks and 12 weeks, however the entire control group withdrew following the 3 week follow-up visit, and so we opted to include only the 3 week data in our

238 analyses for this reason. Sensitivity analyses found that the overall treatment effect seen in figure 4
239 varied greatly with the use of different estimated correlations between baseline and follow-up mean
240 change in pain scores, This is perhaps unsurprising, given firstly that only three studies were able to
241 be included in this analysis, and secondly since two thirds of the included studies had imputed data
242 (and therefore were subject to change in the sensitivity analyses).

243

244 **Effect on function**

245 The secondary outcome of interest was effect of hip IASI on function. Of the 4 studies to assess
246 function using subjective outcome measures 3 noted a statistically significant improvement in
247 function in the steroid group compared to control.[12,13,15] These included a significant
248 improvement in modified Katz ADL index at 3 weeks post injection,[16] WOMAC function subscale
249 score[12,13] and SF-36 physical and social functioning subscales[12] at 8 weeks post-injection.
250 Atchia *et al*[13] reported the magnitude and duration of the effect of hip IASI on WOMAC function
251 subscale largely mirrored the effect on pain. At 1 week post-injection the SMD was large at 1.3,
252 decreasing to 0.9 at 4 weeks, and 0.4 at 8 weeks with less marked reduction in efficacy reported by
253 Lambert *et al*.[12] Two trials assessed hip ROM as an objective measure of hip function although
254 the results were inconsistent. In one trial a very large and statistically significant increase in hip
255 ROM was present at 3 weeks post hip IASI[16]; however, the only other study to assess ROM did
256 not identify any significant difference at either 4 or 8 weeks post-injection.[12]

257

258 **Safety of hip IASI**

259 Four trials reported safety data.[12.13,15,16] Only one serious adverse event, a deep venous
260 thrombosis 3 months post-injection, was reported in the IASI group.[12] The injection procedure
261 itself was noted to be well tolerated.[12,13,15,16] No adverse events in the IASI group were
262 reported by two trials.[12,15] The third trial found similar rates of adverse events (52% placebo

group vs. 51% in the IASI group), and noted that 'most were mild and/or considered unrelated to treatment.'[12] Qvistgaard *et al* noted that 3 patients (out of a total sample of 101) experienced a flare in pain post-injection but did not allocate these to a specific treatment group.[15]

DISCUSSION

The evidence from this review suggests that hip IASI may be efficacious in delivering short term, but clinically significant, pain reduction in those with hip OA, and may also lead to transient improvement in function. The treatment effect appears to be of rapid onset with a large treatment effect size reported at 1 week post-injection. The magnitude of pain reduction and functional improvement decreases thereafter, although two trials report clinically significant differences in both pain and function at 8 weeks post-injection.[12,13] This pattern is similar to that observed in studies of IASI at other sites in OA, such as the knee.[8]

Because each trial used a different preparation or dose of steroid it was not possible to determine the effect of any particular dose on outcome. The injection procedure itself was well tolerated by trial participants[12,13,15,16] and only 1 serious adverse event in those receiving an IASI was reported.[12]

This is the first systematic review to address the effect of hip IASI on pain and function. It utilised a broad and systematic search strategy to identify all the available evidence. There were nonetheless some limitations which need to be considered. As noted by the ACR guidelines expert panel, the number of studies performed in those with symptomatic hip OA is very small[5] and the review's conclusions are based on the results of 5 trials containing only 346 participants in total. Small trials are recognised to potentially over-estimate treatment effect sizes,[46] or report a significant effect when none is present.[47] Thus a degree of caution is required in interpreting the results and it is not possible to draw firm conclusion on the efficacy of IASI in hip OA. The lack of available data made it difficult to undertake any formal assessment of this potential bias on treatment effect. All of the included trials were also of short duration and it remains unclear for how long hip IASI exert a clinically meaningful effect. Additionally, the majority of participants were awaiting, or eligible for, a THA, which suggests that these participants had severe OA and so caution is needed in generalising these findings to those with less severe disease.

The trial populations, consisting predominantly of those with severe hip OA, and the availability of an alternative effective treatment (THA) for this group, resulted in challenges in the conduct of the included trials. These included difficulties in recruitment leading to trials being stopped prior to recruiting the pre-specified sample size,[12] withdrawal of all controls prior to the primary end point due to inefficacy of the control treatment[16] and reduction in follow up duration due to participants undergoing THA[13] potentially increasing the risk of bias. We also cannot exclude publication bias in which trials that failed to show a treatment effect for IASI may have been less likely to have been published. Although we did search clinical trial registers and found only one, potentially ongoing, unpublished trial suggesting there is unlikely to be significant recent publication bias, we cannot exclude publication bias pre-dating the requirement for clinical trial registration.

A large number of different pain and function outcome measures were utilised across the included trials. This significant heterogeneity in methodology between trials, coupled with the limited reporting of trial statistics, particularly for individual time points, limited the pooling of results into treatment effect sizes (standardised mean difference), in turn rendering it difficult to compare results between trials other than the limited fixed-effects odds-ratio estimate of OMERACT-OARSI responders, using the 8 week time point from two of the included trials and for an overall SMD in only three trials.. This highlights the importance of developing and use of core outcomes for clinical trials in this area.

This review only included RCTs which incorporated a placebo group and thus did not consider trials comparing different doses of steroid or those comparing steroids with other treatments such as hyaluronic acid (HA) preparations. Whilst this did reduce the number of included trials, placebo effects are expected to be large in trials of injections in osteoarthritis, and this (large) effect would confound any observed treatment effect, making results less clear than in the present review.[48] Additionally, there is a lack of evidence on the efficacy of HA compared to placebo in the hip[49] and studies of HA in the knee suggest there are marked variations in treatment effect size for different preparations[50] adding significantly to the heterogeneity.

This review, is consistent with the recent Cochrane review of IASI in knee OA with regards the overall quality of the evidence, heterogeneity between trials and evidence of small study effects[8] and highlights the need for further research to confirm both the efficacy and the short and long term safety in IASI in the management of hip OA. Future trials should be sufficiently large and include a placebo group. Standardised outcomes such as those such as those recommended by OARSI[51] should be used and the results should be presented in a manner which will facilitate inclusion in future meta-analyses.

In conclusion, hip IASIs, when performed with image guidance appear to be well tolerated and may be effective in reducing pain and improving function in the short term in those with severe hip OA, though the quality of the evidence is relatively poor. Further large, methodologically rigorous trials are required to verify whether intra-articular corticosteroids are beneficial and for how long.

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AUTHOR CONTRIBUTION

Conception and design: PSM, DF, TWO, Literature search: PSM, Data extraction: PSM, NM Analysis and interpretation of data: PSM, MJP, NM, DF, TWO, Drafting of article: PSM, MJP, TWO. All authors contributed to the critical revision of the manuscript and approved the final version.

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CONFLICT ON INTERESTS

The authors declare they have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram

Figure 2. Summary of pain outcome measures results by time since injection for included trials

Figure 3. Forest plot of fixed-effects Mantel-Haenszel estimate of number of OMERACT-OARSI Responders at 8 weeks post hip intra-articular steroid injection

Figure 4. Forest plot of random-effects Mantel-Haenszel estimate of mean pain outcome change post hip intra-articular steroid injection, in the 3 studies providing appropriate data.

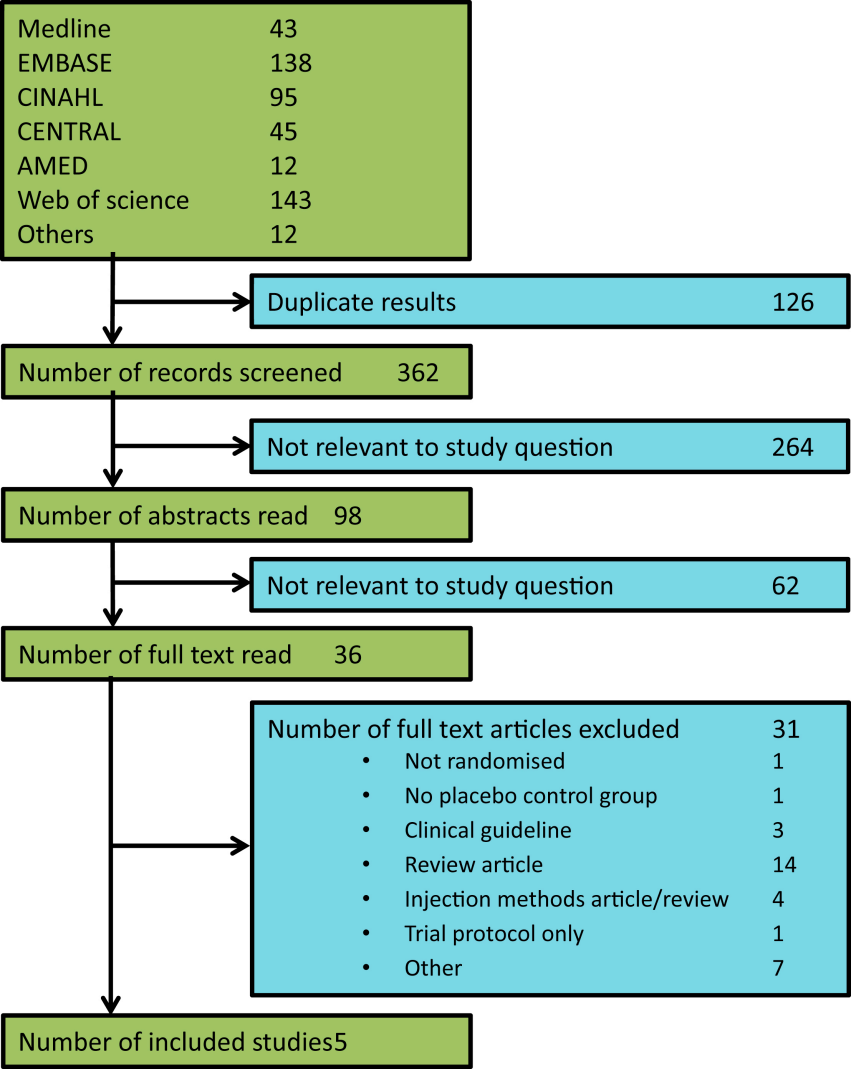
Table 1. Summary of the characteristics and results of studies meeting the inclusion criteria.

Reference	Setting	Sample Size [number receiving IASI]	Mean age, years	Study population	OA definition	Intervention groups	Injection guidance	Follow up, weeks	Primary pain outcome*	Funding
Flanagan *et al* 1988 [14]	Essex, UK	35 [12]	range 46-79	Awaiting THR for OA	Charnley	20mg Triamcinolone† + 0.5% Bupivicaine 0.5% Bupivicaine Saline	Fluoroscopy	4, 8, 12, 26	NRS 1-5	Not stated
Kullenberg *et al* 2004 [16]	Karlshamn, Sweden	80 [40]	70	Awaiting THR Ahlback criteria ≥2 and JSN with cartilage destruction ≥ 50% Pain at rest and on weight bearing ≥ 3 VAS	Ahlbäck	80mg TA 1% Mepivacaine	Fluoroscopy	3, 12	VAS - pain on weight bearing	Not stated
Qvistgaard *et al* 2006 [15]	Copenhagen, Denmark	101 [32]	66	Pain at randomisation Stable medication for 3 week	ACR	40mg MP + 2 sham injections 3x Hyalgan 3x Saline Injection repeated at 14 day intervals	Ultrasound	2, 4, 12	VAS-pain on walking	Oak Foundation, Erna Hamilton Foundation and Fidia Inc.
Lambert *et al* 2007 [12]	Alberta, Canada	52 [31]	62	Symptoms for ≥ 6 months Persistent pain despite paracetamol±NSAIDs	ACR	40mg TH + 0.5% Bupivcaine 0.5% Bupivicaine + Saline	Fluoroscopy	4, 8	WOMAC20	CHAR/NycoMed, MSI foundation, Arthritis Society of Canada, University of Alberta Foundation
Atchia *et al* 2011 [13]	North Tyneside, UK	77 [19]	69	Unilateral hip OA Pain >1 month Listed for THR or NZ priority score ≥20	ACR	120mg MP + 1% Lidocaine Durolane + 1% Lidocaine Normal saline + 1% Lidocaine Standard care - no injection	Ultrasound	1, 4, 8	NRS worst pain	National institute of Health Research and National Health Service

* Where no primary pain outcome was specified the highest ranked pain measures reported in the hierarchy suggested by Juni *et al* [1]was utilised. † Triamcinolone salt not specified.
Abbreviation: IASI – intra-articular steroid injection, MP – Methylprednisolone Acetate, NRS - Numerical rating scale, OARSI-Osteoarthritis research society international, THR - total hip replacement, TA - Triamcinolone Acetonide, TH - Triamcinolone Hexacetonide, MP – Methylprednisolone ?acetate, NSAIDs – Non-steroidal anti-inflammatory drugs, JSN – joint space narrowing, ACR – American College of Rheumatology, VAS - Visual analogue scale, NRS – Numerical rating scale, WOMAC- Western Ontario and McMaster University osteoarthritis index. WOMAC20, 20 % reduction from baseline in WOMAC pain subscale.

Table 2. Quality assessment of included trial using the Jadad scoring method.

Reference	Randomised	Randomisiation is described and appropriate	Double blind	Method of double blinding described and appropriate	Description of withdrawals and drop outs	Total Jadad Score
Flanagan *et al* 1988 [14]	Yes	Not reported	Yes	Yes	No	3
Kullenberg *et al* 2004 [16]	Yes	Yes	Yes	Yes	No	4
Qvistgaard *et a*l 2006 [15]	Yes	Not reported	Yes	Yes	Yes	4
Lambert *et al* 2007 [12]	Yes	Yes	Yes	Yes	Yes	5
Atchia *et al* 2011 [13]	Yes	Yes	No	N/A	Yes	3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AMED 12
Web of science 143
Others 12
Duplicate results 126
Number of records screened 362
Not relevant to study question 264
Number of abstracts read 98
Not relevant to study question 62
Number of full text read 36
Number of full text articles excluded 31
Not randomised 1
No placebo control group 1
Clinical guideline 3
Review article 14
Injection methods article/review 4
Trial protocol only 1
Other 7
Number of included studies5

FIGURE 2.

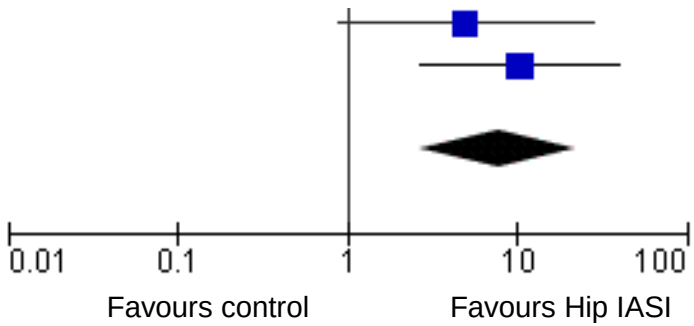
Reference	3-4 weeks							8 weeks							12 weeks							Summary
	VAS pain on walking	VAS pain at rest	WOMAC pain	NRS worst pain	Lequesne score	Patient global assessment	OARSI responder criteria	VAS pain on walking	VAS pain at rest	WOMAC pain	NRS worst pain	Lequesne score	Patient global assessment	OARSI responder criteria	VAS pain on walking	VAS pain at rest	WOMAC pain	Lequesne score	Patient global assessment	OARSI responder criteria		
Flanagan *et al* 1988*																						9/12 in steroid group vs. 14/24 control reported pain improved at 4 weeks. No statistics reported.
Kullenberg *et al* 2004†	✓	✓																				Steroid group VAS pain on walking and at rest reported to be significantly different to control at 3 weeks. No p value reported.
Qvistgard *et al* 2006	✓	×			×	×	×								×	×		×	×	×		Pain on walking steroid group effect size 0.6 (95% CI:0.1-1.1) across all time points. Difference between placebo and steroid $P_{4\ weeks}$=0.006 $P_{12\ weeks}$=0.58.
Lambert *et al* 2007			✓			✓				✓			✓	✓								OARSI responder criteria: 22/31 in the steroid group vs. 4/21 control at 8 weeks, p<0.01.
Atchia *et al* 2011			✓	✓			✓			✓	✓			✓								OARSI responder criteria: 7/19 in steroid group vs. 2/19 in control group at week 8, p=0.02.

✓ statistically significant improvement compared to control (at an alpha level of 0.05). × no statistically significant improvement compared to control . Grey box – results not considered at this time point. * No statistical comparison between controls and steroid group reported † Data from subsequent time points excluded due to absence of control group at later time points. Abbreviations: NRS - Numerical rating scale, OARSI-Osteoarthritis research society international, VAS - Visual analogue scale, WOMAC- Western Ontario and McMaster University osteoarthritis index.

FIGURE 3.

Study	Hip IASI Responders	Hip IASI Total	Control Responders	Control Total	Weight	M-H, Fixed, 95% CI
Atchia *et al* 2011	7	19	2	19	47.70%	4.96 [0.87, 28.15]
Lambert *et al* 2007	22	31	4	21	52.30%	10.39 [2.73, 39.56]
Total (95% CI)		**50**		**40**	**100%**	**7.80 [2.70, 22.48]**
Total responders	29		6			

Heterogeneity: Chi^2 =0.44, df=1 (p=0.51); I^2=0%
Test for overall effect Z=3.80 (P=0.0001)

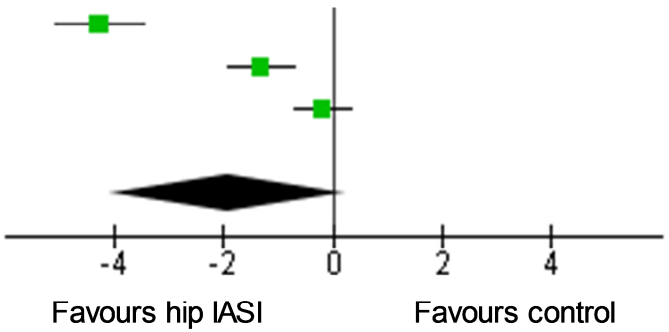


Responders were those meeting the OMERACT-OARSI response criteria. Abbreviations: IASI - intra-articular steroid injection, M-H Mantel Haenszel.

FIGURE 4.

Study	Follow up period	Weight	Effect size (SMD) [95% CI]
Kullenberg *et al* 2004	3 weeks	32.8%	-4.27 [-5.08, -3.46]
Lambert *et al* 2007	2 months	33.5%	-1.31 [-1.92, -0.70]
Qvistgaard *et al* 2001	90 days	33.7%	-0.19 [-0.70, 0.33]
Total		**100%**	**-1.90 [-4.07, 0.26]**

Heterogeneity: Tau^2=3.54; Chi^2=69.90, df=2 (p < 0.00001); I^2=97%
Test for overall effect *Z*=1.73 (P=0.08)



Abbreviations: SMD - standardised mean difference, IASI - intra-articular steroid injection