Efficacy and safety of multiple intra-articular corticosteroid injections for osteoarthritis – a systematic review and meta-analysis of randomised controlled trials and observational studies

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Abstract

Objectives
To investigate the efficacy and safety of multiple intra-articular corticosteroid (IACS) injections for the treatment of osteoarthritis (OA).
Methods
We conducted electronic searches of several databases for randomised controlled trials (RCTs) and observational studies. Standard Mean Difference (SMD) was calculated for efficacy whereas hazards ratio (HR) was used for adverse effects. Results were combined using the random effects model. Heterogeneity was measured using I^2 statistics.
Results
Six RCTs were included for efficacy assessment. The use of multiple IACS appeared to be better than comparator (SMD for pain -0.47, 95% CI -0.62 to 0.31). However, there was considerable heterogeneity (I^2 92.6%) and subgroup analysis by comparator showed no separation of regular IACS from placebo, though timing of pain assessments was questionable. Fourteen RCTs and two observational studies were assessed for the safety of multiple IACS. Minor local adverse events were similar in both groups. One RCT found that regular IACS every 3 months for 2 years caused greater cartilage loss compared to saline injection (-0.21mm vs 0.10mm). One cohort study found that multiple IACS injections associated with worsening of joint space narrowing (HR 3.02, 95% CI 2.25 to 4.05) and increased risk of joint replacement (HR 2.54, 95% CI 1.81 to 3.57).
Conclusion
Multiple IACS injections are no better than placebo for OA pain according to current evidence. The preliminary finding of a detrimental effect on structural OA progression warrants further investigation. Efficacy and safety of multiple IACS reflecting recommended best practice has yet to be assessed.

Key messages:
- Repeated IACS injections on pain relief did not appear statistically different to that of comparator
- Some evidence does demonstrate potential detrimental effects of multiple IACS injections
- Data from studies with more pragmatic designs will better inform clinical practice

Keywords: osteoarthritis, joint injections, corticosteroid, placebo, hyaluronic acid, pain, cartilage.

1 Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide and is becoming more prevalent with the increasing age of the population [1, 2]. The impact of OA can lead to chronic pain, reduced function, participation restriction and reduced quality of life [2, 3]. In turn this can have a significant impact on an individual's employment and a recent survey reported up to 15% of people with OA taking earlier retirement of up to 8 years [3].

A step wise management approach has been recommended by the National Institute of Health and Care Excellence (NICE) [4]. Non-pharmacological interventions including patient education, strengthening and aerobic exercise, weight reduction if overweight, and reduction of adverse mechanical factors are core interventions. Pharmacological treatments are regarded as adjuncts; to be added in if required specifically for pain relief. Paracetamol and topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are recommended first before oral NSAIDs or weak opioids [4]. Despite this many people with OA still experience persistent pain (up to 70%) [3] and thus end up with frequent visits to healthcare professionals.

Intra-articular corticosteroid (IACS) injections are one of the treatments often used in primary and secondary care for patients with severe OA pain which is inadequately alleviated by other analgesics. This practice has been supported by studies showing that single steroid injections can reduce pain and improve function significantly, especially in the short-term [5]. IACS injections are often reserved for more ''end-stage'' OA, especially in joints showing clinical signs of inflammation (e.g. effusion), prior to consideration of surgical interventions. If an injection is successful at relieving pain, but symptoms subsequently worsen again, repeat injections may be considered but at a generally agreed maximum frequency of no more than four per year into the same joints [6].

The pathogenesis of OA is thought to have an inflammatory component [7]. Hence one rationale for IACS is to suppress inflammation and reduce articular damage [8]. It was previously thought that the effect of IACS would be a positive effect on cartilage health and integrity [9]. However, there is emerging evidence that suggests cartilage volume loss with multiple IACS [10, 11]. In clinical practice as IACS injections are often given serially if they improve patient symptoms, we undertook this systemic review to summarise the literature for the two key clinically relevant questions: are multiple IACS injections effective for OA pain and are they safe?

2 Methods

2.1 Search strategy

Systematic literature searches were performed in January 2019 using the databases MEDLINE, EMBASE, AMED, Web of Science, PubMed, Cochrane Library, and Google Scholar. Relevant references were also explored. A structured search strategy was used for both efficacy (see appendix) and safety. Data extracted included study design characteristics, participant details, characteristics of IACS (including dosage, frequency and duration of treatment), comparator used and outcomes examined. Any discrepancies were resolved through discussion of papers by the reviewers.

2.2 Eligibility criteria

We used the following criteria to select studies:

Patients	Patients over age of 18 with clinically and/or radiographically-defined OA

Intervention	Multiple intra-articular steroid injections
Comparator	No treatment, placebo (e.g. normal saline) or active control (e.g. hyaluronic acid)
Outcomes	Pain relief and adverse effects

The inclusion criteria were based on the above PICO where patients were from 1) RCTs of multiple use of IACS in clinically and radiographically-defined OA at any site, and 2) observational studies of clinically-defined OA at any site. The intervention used included all types of corticosteroid injections e.g. depomedrone, triamcinolone, and beclomethasone. Studies with single IACS were excluded. We excluded all non-OA joint pathology (e.g. rheumatoid arthritis, gout). The comparator was either placebo (e.g. normal saline), active control (e.g. hyaluronic acid) or no injection. Efficacy in terms of pain relief was assessed using RCTs, whereas adverse effects were assessed using both RCTs and observational studies. There was no language limitation for this study

2.3 Quality assessment

The quality of RCTs were assessed using the Cochrane risk of bias tool [12]. The two components of randomisation reviewed were generation of random allocation sequences and concealment of allocation. We considered trials if sequencing was clearly randomised, such as by computer generated random sequence. We considered concealment adequate if participants and investigators responsible were unable to suspect allocation of treatment. The quality of observational studies was not assessed.

2.4 Data management and extraction

Potentially eligible papers were screened using title and abstracts by the main investigator (SA). They were then downloaded to Endnote and their eligibility assessed using PICO. The first author (SA) extracted the data using Microsoft Excel. A second author (JK) validated the data and any disagreement was discussed and resolved with a third author (WZ). The following information was extracted: publication details, including author, journal, year and publication type, trial, study design, blinding and duration and participant details and demographics. The type of corticosteroid dose and frequency were extracted. Where possible changes from baseline pain scores were extracted and the differences between groups were calculated. If sufficient data could not be extracted from the publication the study authors were contacted for missing data.

2.5 Synthesis of results

Mean and standard deviation (SD) for pain scores at baseline and end-point for individual studies were used to calculate the mean reduction in pain in each group. The primary end point was the longest time point of the study if there were multiple points. The Standardised Mean Difference (SMD) then was calculated between groups. Further subgroup analysis based on different time points was undertaken as appropriate.

The hazards ratio (HR) was used for adverse effects if possible; otherwise they were presented as measured. A random effects model was used to pool the data. Heterogeneity was measured using I^2 statistics.

3 Results

There were two literature searches. For efficacy 1410 citations studies were identified in the initial search and after removal of duplicates 649 studies were identified (Figure 1). Overall six RCTs met our inclusion criteria. An overview of their characteristics is shown in Table 1. For safety data, 514 studies were identified after removal of duplicates (Figure 2). Overall fourteen RCTs and two observational studies were included. An overview of their characteristics is shown in Table 2.

3.1 Characteristics of included studies

Of the six RCTs [13-18] which met the inclusion criteria for efficacy assessment, four used hyaluronic acid and two used normal saline (placebo) as the comparator. Corticosteroids used were betamethasone (three RCTs); triamcinolone (two RCTs) and methylprednisolone (one RCT). The mean age across these 6 RCTs was 61.4 years with 70.4% of participants being women. The number of IACS injections varied from 2 to 8. Dosing interval varied from once a week to once every 12 weeks (Table 1). Pain scores were calculated at different time points e.g. Davalillo et al [15] measured pain scores at Week 0, 13, 26, 39 and 52, whereas Monfort et al [17] measured the pain score at week 0, 1, 2, 4, 12, 24.

Of the total fourteen RCTs [19-28] and two observational studies which met the inclusion criteria for safety assessment, there was greater variation in type of IACS used, although just under half used methylprednisolone (Table 2).

3.2 Risk of bias

The assessment of risk of bias for RCTs is presented in Table 3. Overall, randomisation was performed in the majority of studies, but 8 RCTs were unclear concerning allocation concealment [13, 17, 18, 21, 22, 23, 25, and 26].

3.3 Efficacy

Figure 3 presents our overall analysis of VAS Pain scores from baseline to study end-point (which varied in all studies). It would appear that IACS was more effective in pain reduction than the comparator (SMD -0.47, 95% CI -0.62, -0.31). An I^2 statistic of 92.6% indicates a great deal of heterogeneity. However, one study stood out strongly in favour of IACS [15] (SMD -1.63, 95% CI -1.95, -1.31), as an outlier. After removing this trial, the difference became statistically insignificant (SMD -0.12, 95% CI -0.29, 0.06), with improved heterogeneity (I^2 0.00%, p value 0.444).
Figure 4 shows the subgroup analysis according to varying time points at 6, 12, 26, 52 and 106 weeks. Apart from pain reduction at 26 months (SMD -0.55, 95%CI -1.06, -0.05), no difference was observed between IACS and comparator.
At 6 weeks 3 studies were included and showed that the overall pain score did not differ between the two groups (SMD 0.18, 95% CI -0.13, 0.49). At 12 weeks 3 studies were included with no difference in pain scores between IACS and placebo, and with a wide confidence interval (SMD 0.26, 95% CI -1.12, 1.63). At 26 weeks where 4 studies were included, the VAS score was better in the IACS group (SMD -0.55, 95% CI -1.06, -0.05). At 52 weeks 3 studies were included and showed no difference in pain scores (SMD -0.55, 95% CI -1.69, 0.58). At 104 weeks only two studies and showed no difference in the baseline and endpoint VAS scores (SMD -0.05, 95% CI -0.32, 0.22).

The individual studies showed a difference in the overall outcome of pain. Bisicchia et al [13] showed an improvement in VAS scores in the IACS group at 6 weeks compared to 12 weeks with HA, however at 1 year follow-up both groups returned to their baseline VAS scores. In

the Bjornland et al study [14] pain scores improved throughout both groups with similar scores. The endpoint for VAS scores were lower in the HA group compared to IACS group. In the Davalillo et al [15] study, pain scores showed a higher reduction in the IACS vs placebo groups especially at 3 months post initial injection. McAlindon et al [16] showed overall no significant difference in pain scores over the 2 years with an analysis for repeated outcomes every 3 months. Monfort et al [17] reported overall improvement of VAS scores in both groups with the most pain relief being at week 4. After this the VAS increased in both groups but with an overall reduction from the initial values. Raynauld et al [18] showed no statistical difference for pain reduction between the two groups.

A subgroup analysis was undertaken according to normal saline or HA as a comparator. The 4 RCTs using HA as control showed that IACS was more effective in pain reduction than HA (SMD -0.77, 95% CI -0.96, -0.57). However, there was considerable heterogeneity (I^2 93.9%) when results from Davalillo et al [15] were included. In contrast the 2 RCTs using normal saline as a control demonstrated that multiple IACS injections were no better than placebo for pain relief (SMD -0.05, 95% CI -0.31, 0.22). The I^2 result was 0% with p value of 0.724.

3.4 Safety

3.4.1 Evidence from RCTs

Local side effects such as temporary joint pain, erythema, and itching were reported in some but not all RCTs. As the events were rare per study, it is not possible to calculate HR for each trial. There were no reports of joint infection. Serious adverse events were reported in one study by Fusch et al [20] in which one participant in the IACS group experienced malaise, tachycardia and hypotension after the first injection and had to withdraw from the study.

Raynauld [18] examined radiographs at baseline, 1 and 2 years and found 'no difference between the treatment groups.' However, McAlindon [16] recorded a greater cartilage volume loss on MRI in the index compartment in the IACS group compared to placebo (mean change in cartilage loss -0.21mm vs -0.10mm) and a higher cartilage damage index over 2 years.

3.4.2 Evidence from observational studies

Wada et al [27] followed patients over 9-12 years and used plain radiographs to assess the tibiofemoral joint. They noted no difference in radiographic degeneration in 11 out of 24 knees treated with IACS compared to 43 out of 82 knees in the no injection group.

More recently Zeng et al (2019) [28] undertook a cohort study using the Osteoarthritis Initiative database. They found that the use of multiple IACS over 48 months was associated with an increased risk of cartilage loss and joint replacement (adjusted as a competing event). They reported that 65 of 148 (44%) knees in the IACS group showed worsening of OA compared to 80 out of 536 (15%) knees in the control group (using Kellgren-Lawrence grade for the tibiofemoral joint). The HR for worsening OA was 4.67 (95% CI 2.92,7.47). They also reported, over the course of the observational study, 33 joint replacements in the IACS group (22.3%) compared to 29 in the placebo group (5.4%).

4 Discussion

This systemic review and meta-analysis found that the effect of repeated IACS injections on pain relief in people with OA did not appear statistically different to that of the comparator (saline or hyaluronic acid) at the end of the study. However, frequent pain assessments were not undertaken during the course of the trials (including the periods shortly following injections) so it is impossible to determine from the studies identified whether overall pain control during the study period was benefited by serial IACS injections. Furthermore, the design of these studies does not reflect clinical practice since regular three-monthly injections irrespective of patient symptoms is not a recommended schedule. With respect to safety, repeat IACS injections appear generally safe apart from concern over possible accelerated joint cartilage loss. Unfortunately, data on this are sparse. One placebo-controlled RCT assessing knees by MRI reported cartilage loss from three-monthly IACS injections over two years, whereas a smaller two year placebo-controlled RCT using a similar injection frequency found no effect on structural changes determined radiographically. One propensity score-matched cohort study reported more radiographic progression and increased risk of joint replacement in people receiving multiple IACS injections, but cannot completely overcome the issue of confounding by indication (i.e. those with more severe symptomatic OA and potentially worse prognosis receive injections). A propensity score matched design for an observational study can only control known confounding factors. An RCT is therefore still needed to control unknown/unmeasured confounding factors.

The use of IACS in OA management is supported by results from single injection placebo-controlled RCTs, though the evidence is heterogeneous and predominantly from older studies of low quality [29, 30]. Although most benefits occur in the first few weeks following injection, more prolonged improvements are also recorded [30, 31]. For example, one RCT comparing triamcinolone hexacetonide and methylprednisolone acetate for people with knee OA (n=100) noted long-lasting improvements, with over 70% of participants still achieving OMERACT-OARSI responder criteria 24 weeks post-injection [31]. Frizziero and Ronchetti [19] examined synovial membranes after injections of both corticosteroid and hyaluronic acid into knee joints and noted a decrease in inflammation of the synovial membrane. However, animal studies have highlighted deleterious histological changes in cartilage after IACS injections with a decrease in proteoglycan content and cartilage volume [32] and this has been hypothesised to possibly contribute to progression of cartilage loss in humans [33]. A recent retrospective observational study by Simeone et al [34] reviewed outcomes 3-10 months after single IACS injection of hip joints with OA and reported that 44% had radiographic progression of OA compared to 24% of hip OA controls without the injection and that 17% versus 1%, respectively, developed femoral head collapse. The longitudinal studies by Wada at al [27] and Zeng et al [28], more recently show higher rates of OA progression and joint replacement in the IACS group. However, the imaging focused only on the tibio-femoral (TF) compartments (an index TF compartment was chosen) rather than all 3 compartments. If IACS was to cause cartilage attrition, this might be expected to affect all 3 compartments of the knee, but this was not examined in these studies. Another updated review on IACS in hip and knee OA has been published by Kompel et al in 2019 [35]. They reviewed specific side-effects in those receiving IACS of hip or knee joints. Overall 8% of participants experienced side-effects (receiving a mean of 1.4 injections over a mean time period of 7 months) and of these 6% had progressive OA, 0.9% suffered subchondral insufficiency fractures, and 0.7% suffered from osteonecrosis. They concluded that the use of imaging such as MRI could be helpful (along with patient characteristics) in determining which patients could be at higher risks of such side effects. This concern over the possible effect on cartilage loss from multiple IACS does require a real-life long-term RCT as observational studies are still confounded by indication.

There were some limitations to this systematic review. There was a great deal of heterogeneity in these RCTs. As outlined the dosing intervals were variable ranging from once every week

for 2 weeks, to once every 12 weeks for 52 weeks. Also the steroid used was different. This does represent to some degree real life practice wherein different regimes are used. The studies crossed different time periods; additionally VAS time points varied from one study to another (table 1). We emailed authors to obtain original study data. However, as this was not received we used the baseline scores, 52 week scores and endpoint score in the subgroup analysis. Furthermore different joints were reviewed. 4 out of 6 RCTs used the knee but 1 study used the 1st CMC joint and another included the temporomandibular joint. This could have affected results on pain relief as outcomes from OA vary between joints as they are biomechanically different, in particular weight-bearing joints which may give more pain. Generally, the study sample sizes were small ranging from 40 to 150 total participants. Side-effects were reported differently which were broadly placed in the categories used for our analysis. During the literature review it was noted that more studies have been reported which looked at safety profiles of single IACS.

5 Conclusion

This systematic review included RCTs of regularly repeated IACS injections, using different steroid regimes and different joint sites, and with infrequent pain assessment predominantly undertaken just prior to each injection. This makes it difficult to come to any firm conclusion about the efficacy of multiple IACS injections as they would be administered in the real-life clinical setting. Some evidence does demonstrate potential detrimental effects of multiple IACS injections. However, the cohort data cannot overcome the problem of confounding by indication in that people with more severe/resistant symptoms will receive more IACS injections and be expected to progress more rapidly to joint replacement. Further studies are required to determine the structural safety and efficacy of multiple IACS injections as given in clinical practice, and not at fixed regular intervals irrespective of symptom severity. Instead, injections should only be repeated at individualised and variable time intervals with a caution of no more than 4 in one year in people who benefit significantly from an IACS injection once their pain/symptoms have returned to more severe pre-injection levels. Data from studies with more pragmatic designs will better inform clinical practice.

Contributions of authors

SA participated in study design, collection of data and the drafting of the article. SA and JK were involved in the analysis and interpretation of the data. Studies that appeared eligible were read by two investigators (SA and JK). WZ conceptualised the study. MD, MH, MHall, SE and WZ participated throughout the study. All authors have participated in regular meetings, interpret, edit and approved the manuscript and article prior to publishing. There was no funding for this systematic review.

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Table 1 Characteristics of studies with efficacy data of multiple IACS

Author Year	Joint	Intervention					Comparator					Time points measured (weeks)
		Number patients	Name	Dose	Number of injections	Interval	Number patients	Name	Dose	Number injections	Interval	
Hyaluronic acid as comparator												
Bisicchia 2016	Knee	75	6-methyl-prednisolone acetate	40mg	2	Day 0 and week 1	75	Hyaluronic acid	Not stated	2	Day 0 and week 1	0, 6, 12, 26, 52
Bjornland 2007	TMJ	20	Betametasone sodium phosphate	Not stated	2	Day 0 and week 1	20	Hylan G-F20	0.7-1ml	2	Day 0 and week 1	0, 2, 4, 26
Davalillo 2015	Knee	91	Betametasoned ipropionate 5mg+ Betametasone sodium phosphate 2mg	5mg +2mg	2	Day 0 and week 4	89	Hyaluronic acid 1%	Not stated	5	Day 0 and weekly thereafter	0, 13, 26, 39, 52
Monfort 2014	1stCMC	40	Betametasone disodium phosphate + Betametasone acetate	1.5mg + 1.5mg	3	Day 0, week 1, and week 2	48	Hyaluronic acid	5mg	3	Day 0, week 1 and week 2	0, 1, 2, 4, 12, 24
Normal saline as comparator												
McAlindon 2017	Knee	70	Triamcinolone	40mg	8	Day 0 and then every 12 weeks	70	0.9 % Normal saline	1ml	8	Day 0 and then every 12 weeks	0, 13, 26, 39, 52, 65, 78, 91, 104
Raynauld 2002	Knee	34	Triamcinolone acetonide	40mg	8	Day 0 and then every 12 weeks	34	0.9% Normal saline	1ml	8	Day 0 and then every 12 weeks	0, 13, 26, 39, 52, 65, 78, 91, 104

TMJ temporomandibular joint; CMC carpometacarpal joint

Table 2 Characteristics of studies with safety data

Author Year	Study design	Joint	Steroid group (a)	placebo (b)	Number of IACS	Duration (weeks)	F/U period (weeks)	Number (a)	Number (b)
Bissachia 2016	Single centre single blind prospective RCT	Knee	6-methylprednisolone	HYADD4	2	1	52	75	75
Bjornland 2007	Randomised, blinded, prospective clinic trial	Temporomandibular	Betamethasone	Hyalun GF20	2	2	26	20	20
Davalillo 2015	Prospective randomized open study	Knee	Betamethasone	Hyalun	2	4	52	98	97
Frizzieo 2002	Randomised open label clinical study	Knee	Methylprednisolone	Hyalun	3	3	25.7	47	52
Fuchs 2006	Prospective active controlled trial	Thumb carpometacarpal	Triamcinolone	Hyaluronic acid	2	5	26	28	28
Grecomoro 1992	Open randomised study	Knee	Dexamethasone + placebo	Sodium hyaluronate	1*	5	8.5	20	20
McAlindon 2017	Double blind clinical trial	Knee	Triamcinolone	Sodium chloride	8	104	104	70	70
Merolla 2001	Retrospective controlled trial	Shoulder	Methylprednisolone	Hyalun GF	3	3	26	33	51
Monfort 2014	Single centre prospective study	Thumb carpometacarpal	Betamethasone	Hyalun	3	3	25	40	48
Pietrogrande 1991	Randomised open label clinical study	Knee	Methylprednisolone	Hyaluronic acid	3	3	8.6	45	45
Qvistgaard 2000	Prospective double blind study three armed parallel group	Hip	Methylprednisolone	Hyalgan or sodium chloride	3	6	12.9	32	69
Raynauld 2003	Double blind controlled trial	Knee	Triamcinolone	Sodium chloride	8	104	104	34	34
Ronchetti 2001	Randomised open label clinical study	Knee	Methylprednisolone	Hyalgan	3	3	26	21	27
Wright 1960	Randomised double blind cross over	Knee	Hydrocortisone	Placebo (not stated)	4	14	10	25	25
Wada 1993	Observational study	Knee	Variable	No injection	Variable	Variable	9- 12 years	8 (14 knees)	53 (82 knees)
Zeng 2019	Multicentre longitudinal observational study	Knee	Variable	variable	variable	48 months	48 months	148	536

*patients in the comparator group received 5 weekly intra-articular injections of sodium hyaluronate- the steroid group had same treatment plan but with the addition of dexamethasone with the first injection

Table 3 Risk of bias

	Random sequence generation	Allocation concealment	Blinding of participants?	Blinding of healthcare providers?	Intention to treat analysis performed?
Bisicchia 2016	Computer generated	Not stated	Not stated	Single blind	Yes
Bjornland 2007	Yes	Yes	Yes	Yes	Yes
Davalillo 2015	Computer generated	Yes	No	No	Yes
McAlindon 2017	Computer generated	Yes	Yes	Yes	Yes
Monfort 2014	Computer generated	Not stated	Yes	Not stated	No
Raynauld 2003	Random number table	Not stated	Not stated	Single blind	No
Frizziero 2002	Computer generated	Yes	Yes	Yes	Yes
Fuchs 2006	'Randomised'- no details given	No	Yes	Yes	Yes
Grecomoro 1992	'Random allocation'- no details given	Not stated	Not stated	Not stated	Yes
Merolla 2001	Not stated	Not stated	Not stated	Not stated	No
Pietrogrande 1991	'Random assignment'- but no details given	Not stated	Not stated	Not stated	Yes
Qvistgaard 2000	'Randomised'- no details given	Yes	Yes	Yes	Yes
Ronchetti 2001	Computer generated	Not stated	Not stated	Not stated	No
Wright 1960	Random number table	Not stated	Not stated	Not stated	No

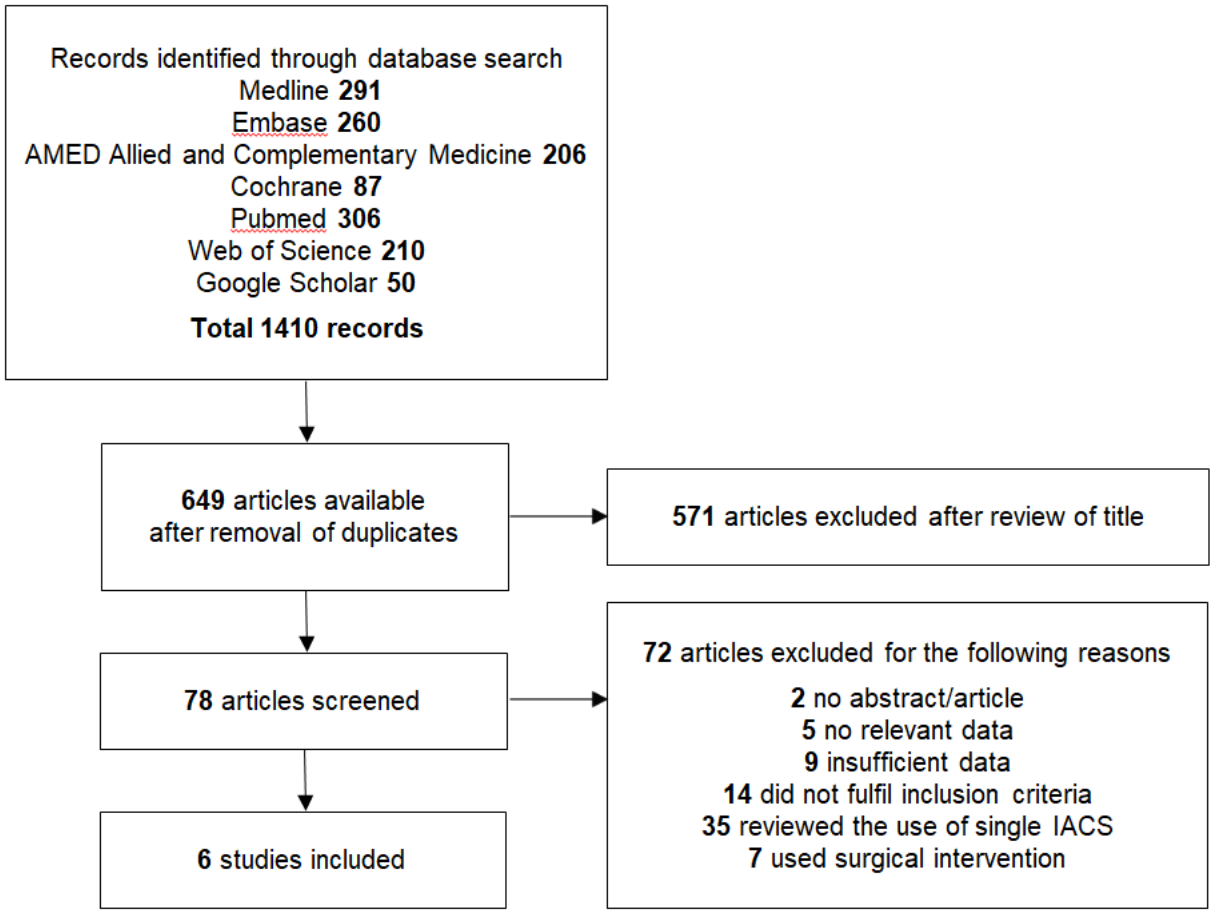

Figure 1 PRISMA flow diagram for efficacy

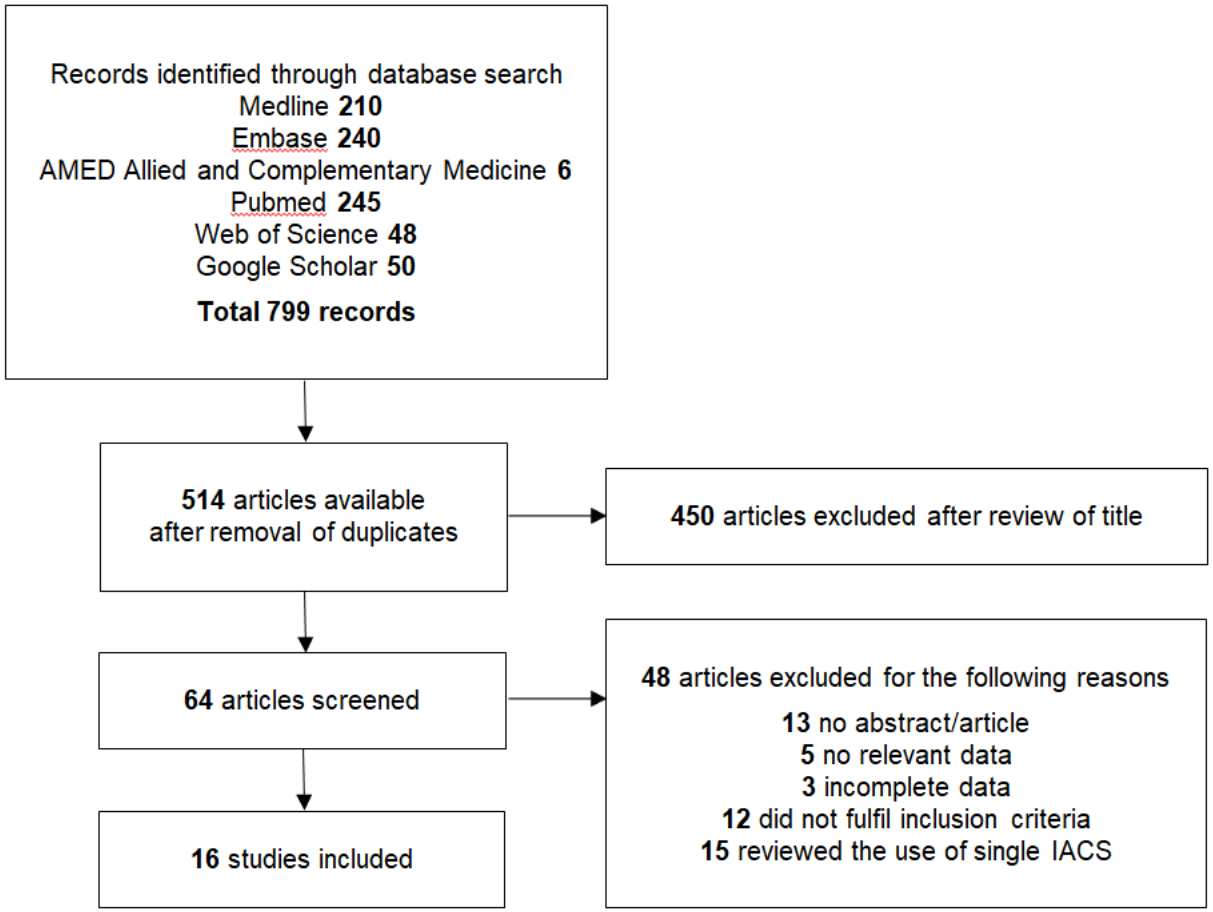

Figure 2 PRISMA flow diagram for safety

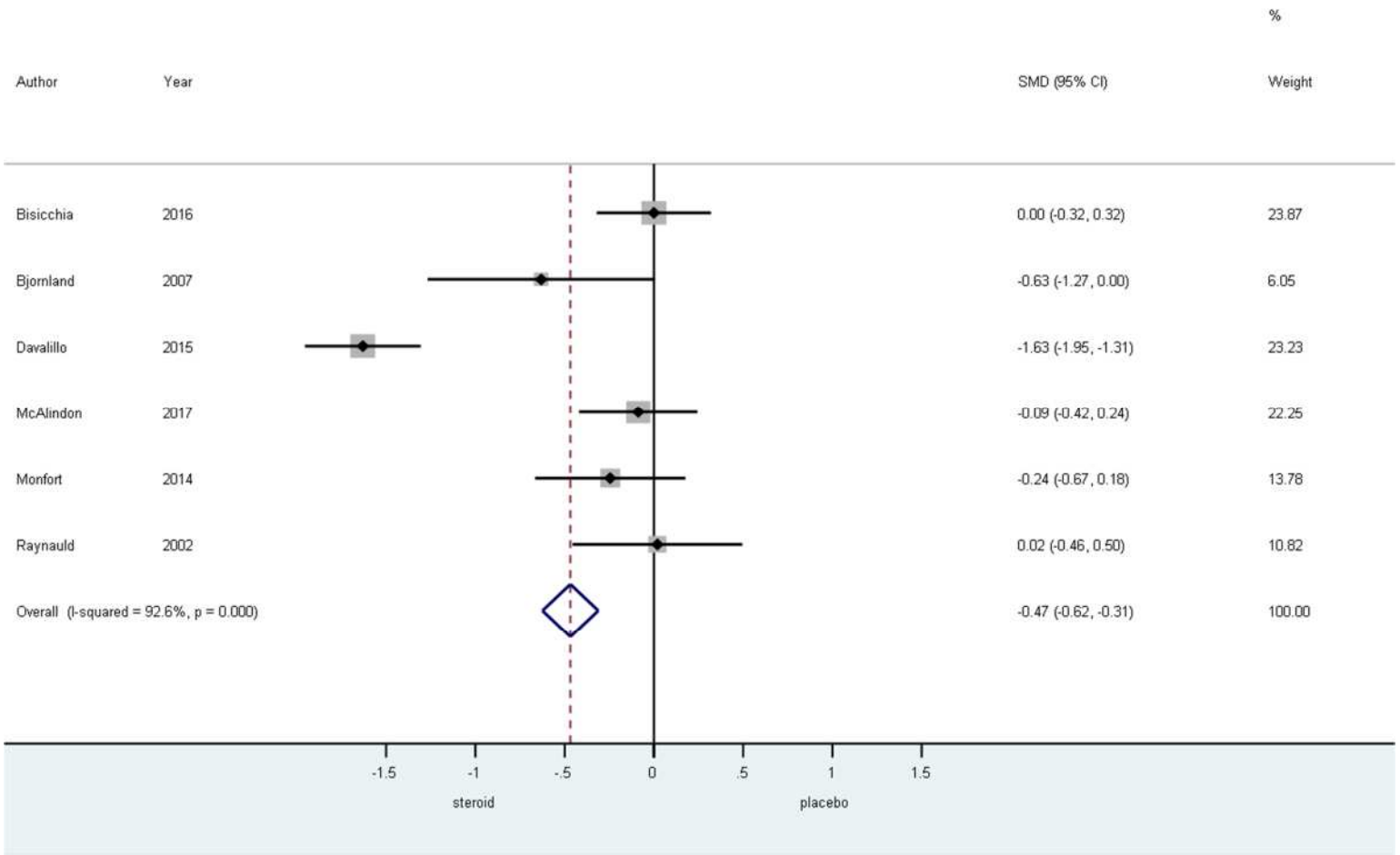

Figure 3 Forest plot of effect size for pain

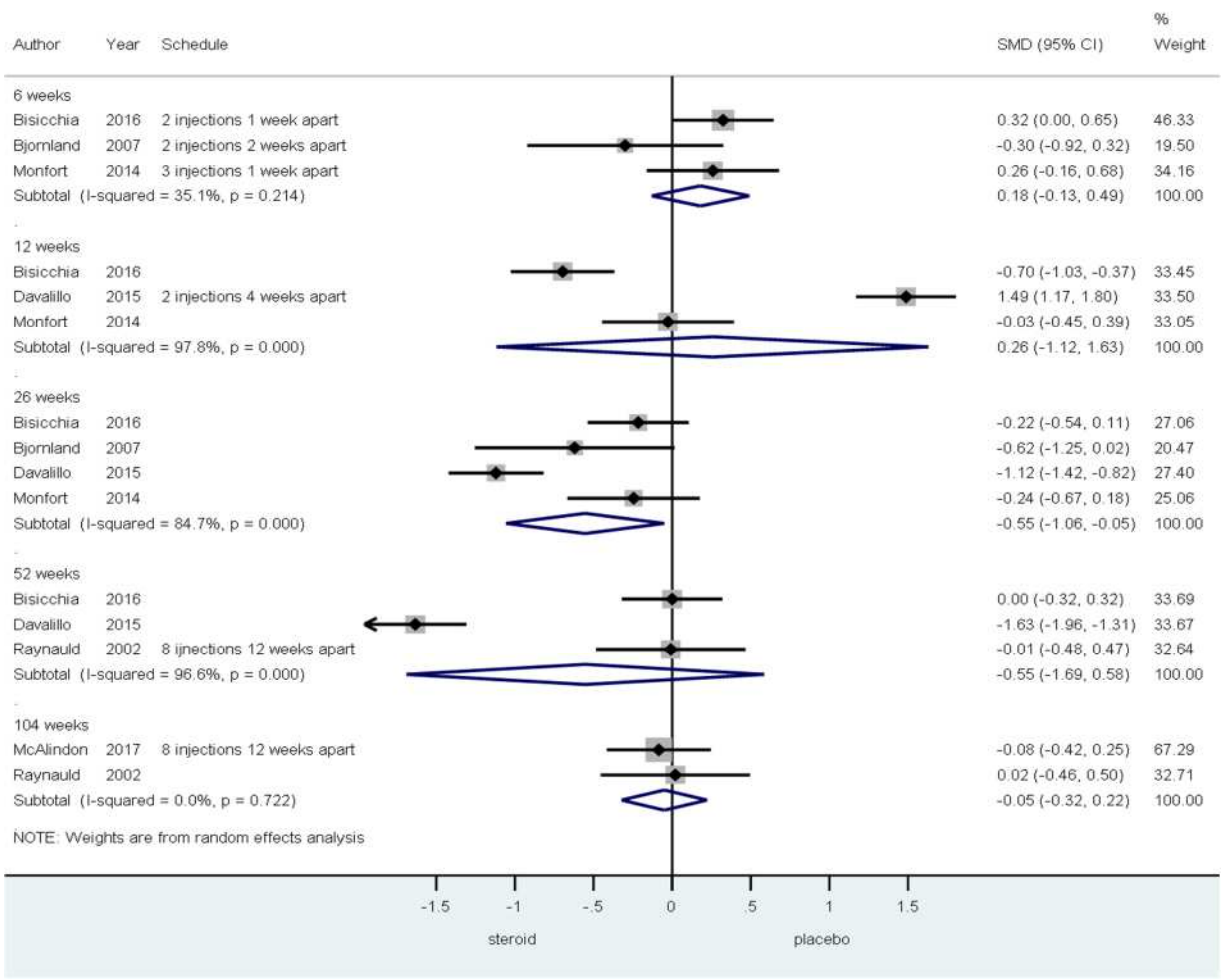

Figure 4 Forest plot of subgroup analysis of effect size for pain at various time points

Appendix- an example of search strategy for efficacy (medline)

1) Randomised controlled trials.mp
2) Randomized controlled trials.mp. or Randomized Controlled Trial/
3) Clinical trials.mp or Clinical Trial/
4) Random allocation.mp. or Random Allocation/
5) Placebo.mp. or Placebos/
6) 1 or 2 or 3 or 4 or 5
7) Osteoarthritis.mp. or OSTEOARTHRITIS/
8) Osteoarthrosis.mp
9) Arthrosis.mp
10) Degenerative arthritis.mp
11) Degenerative joint disease.mp
12) Joint disease.mp. or Joint Diseases/
13) Knee pain.mp
14) Hip pain.mp
15) Hand pain.mp
16) Thumb pain.mp
17) Shoulder pain.mp. or Shoulder Pain/
18) Foot pain.mp
19) Musculoskeletal pain.mp. or Musculoskeletal Pain/
20) Joint pain.mp
21) Arthralgia.mp. or ARTHRALGIA/
22) 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23) Steroid.mp. or STEROIDS/
24) Corticosteroid.mp
25) Glucocorticoids.mp. or GLUCOCORTICOIDS/
26) Triamcinolone Acetonide.mp. or Triamcinolone Acetonide/
27) Triamcinolone Hexacetonide.mp
28) METHYLPREDNISOLONE/ or Methylprednisolone.mp.
29) Prednisolone.mp. or PREDNISOLONE/
30) 23 or 24 or 25 or 26 or 27 or 28 or 29
31) Injection, intra-articular.mp. or Injections, Intra-Articular/
32) 30 AND 31
33) 6 AND 22
34) 32 AND 33