Is it possible to predict which patients are most likely to benefit from intra-articular corticosteroid injections? A systematic review.

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Abstract

Aim:

Intra-articular corticosteroid injections (IACIs) can reduce osteoarthritis-related pain, with differing levels of response across patient groups. This systematic review investigates what is known about the positive and negative predictors of outcomes in patients with osteoarthritis who undergo IACIs.

Methods:

We systematically searched the Medline, Embase and Cochrane databases to May 2023 for studies that evaluated patients undergoing IACIs for osteoarthritis and reported on predictors of outcomes in these patients.

Results:

Eight studies were included. Two were placebo-controlled trials, six were observational studies. Due to the heterogeneity of outcomes and variables between the studies, it was not possible to pool the results for formal meta-analysis. Higher baseline pain, older age, higher BMI, lower range of movement, higher Kellgren-Lawrence radiographic score, joint effusion and aspiration were shown to be predictors of a positive response to IACIs in some of the included studies. However, other studies showed no difference in response with these variables, or a negative correlation with response. Sex, smoking, mental health status, hypertension/ischaemic heart disease, diabetes mellitus, duration of symptoms, and socioeconomic status did not demonstrate any correlation with the prediction of positive or negative outcomes after IACIs.

Conclusion:

Several patient features have been identified as positive predictors of outcomes following IACIs. However, this systematic review has identified inconsistent and variable findings across the existing literature. Further research with standardisation of IACI administration and outcome measures is required to facilitate further analysis of the reliability and significance of predictive factors for response to IACIs.

Keywords:

1. “Osteoarthritis”
2. “Injections, Intra-articular”
3. “Steroids”
4. “Systematic Review”
5. “Correlation of Data”

Introduction

Osteoarthritis is a clinical syndrome of pain within a joint associated with functional limitation and reduced quality of life [1]. It is the most common joint disorder and is a worldwide leading cause of pain and disability. Of those who live to 85, the estimated worldwide prevalence is 24% for knee osteoarthritis and 25% for hip osteoarthritis [2] [3]. The most prominent risk factors for osteoarthritis are increasing age and obesity [4].

The National Institute for Health and Care Excellence (NICE) advise an initial non-pharmacological approach to management with education, exercise, and weight loss. The first line of pharmacological treatment is topical non-steroidal anti-inflammatory drugs (NSAIDs). Intra-articular corticosteroid injection (IACI) is considered for moderate-severe joint pain when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercises [1]. Once the disease progresses, surgical interventions such as joint replacement are considered [5]. Currently, there are no early-stage interventions shown to slow or halt disease progression or restore joint function [6].

The use of IACI for osteoarthritis has been widely researched demonstrating an overall reduction in pain compared to control interventions [7]. However, estimates of the clinical effect are inconsistent with significant variation across trials, and the clinical benefit (especially beyond six weeks) is unclear [8]. Although IACI is generally considered to have few systemic effects, adverse joint events such as osteonecrosis and septic arthritis are still of concern [9] [10]. Despite this, up to 30% of patients have IACIs before total knee replacement [11]. Furthermore, within this cohort of patients, it has been shown that there is an increased

risk of prosthetic joint infection if IACIs are given close to joint replacement surgery [12]. It is, therefore, clinically relevant and important to be able to identify patients in whom IACIs may be of benefit.

Our previous Delphi study involving patients, clinicians and academics identified research priorities for IACIs for osteoarthritis [13]. Fourteen research priorities were identified, one of which was "Is it possible to predict which patients are most likely to benefit from intra-articular corticosteroid injections for osteoarthritis?" To address this research priority, this review aimed to evaluate the existing literature to determine what is known about the positive and negative predictors of outcomes in patients with osteoarthritis who undergo IACIs, and identify areas for future research.

Methods

Data sources and search strategy

The review was registered in the PROSPERO prospective register of systematic reviews (ID: CRD42023427515) and conducted according to a predefined protocol and in line with PRISMA guidelines. We searched for interventional and observational studies which had evaluated patients undergoing IACIs for osteoarthritis and reported on positive and negative predictors of outcomes in these patients. We systematically searched the databases of Medline, Embase and Cochrane (Central) from inception to May 2023. The computer-based searches used a combination of free and MeSH search terms and keywords related to the population (e.g., “osteoarthritis”), and intervention (e.g., “intra-articular corticosteroid injection”). Searches were restricted to the English language. The search was complemented by manually screening the reference lists of all retrieved articles and utilising the “Cited Reference Search” function in Web of Science to obtain any additional studies that were missed by the search strategy. Any previously published systematic reviews and meta-analyses were also screened for studies that met our eligibility criteria. A detailed search strategy has been provided in Appendix 1.

Eligibility criteria

We included studies that met the following PICOS criteria:

- *Population*: adults with osteoarthritis
- *Intervention*: intra-articular corticosteroid injection(s)
- *Comparator*: no comparator, or alternative treatment
- *Outcome*: positive or negative predictors of response to injection(s)

- *Study design*: interventional or observational studies

Study selection and data extraction

Once the searches were completed, the results were imported into Rayyan [14], an online bibliographic tool. One reviewer (RLD) initially screened the titles and abstracts and removed any duplicates to provide a list of potentially relevant articles. Full-text screening of these articles was then performed independently by two reviewers (RLD, VW) against predefined eligibility criteria. Any discrepancies regarding the eligibility of an article were discussed. One reviewer (FES) independently extracted data and conducted risk of bias assessments using a standardised data collection form. A second reviewer (RLD) independently repeated the process to verify the data. A data abstraction table was designed and piloted. Data were extracted on the lead author, year of publication, country of origin, study design, number of participants, joint affected/studied, mean age and body mass index (BMI), proportion of males and females, intervention and/or comparator(s), key outcome measures, predictors of response to IACI, definition of response to IACI, and duration of follow-up. We also extracted data on relevant study characteristics to permit the risk of bias assessments. In circumstances of multiple publications, the study with the most up-to-date or comprehensive information was included.

Risk of bias

The risk of bias within individual RCTs was assessed using the Cochrane Risk of Bias (RoB 2.0) tool, a validated tool for assessing the risk of bias in randomised studies. This tool assesses the risk of bias for the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selective reporting. Each of these

domains is assessed as low risk, some concerns or high risk, and then an overall judgement of the risk of bias is provided for each study. The risk of bias within individual observational studies was assessed using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool, a validated tool for assessing the risk of bias in observational studies. This tool assesses the risk of bias for confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements and selective reporting. Risk is quantified in each domain as low, moderate, serious, or critical risk, and then an overall judgement of the risk of bias is provided for each study.

Data analysis

Due to the nature of the data, formal meta-analysis and statistical techniques were not appropriate. Therefore, a narrative review has been provided.

Results

Study selection

Our systematic search strategy yielded 4,368 records, which were reduced to 3,717 after duplicates were removed. After the initial screening of titles and abstracts, 448 full-text articles required detailed evaluation. Of these, 436 of these failed to meet our inclusion criteria, leaving eight studies eligible for inclusion in this systematic review. A PRISMA flow diagram is provided in Figure 1.

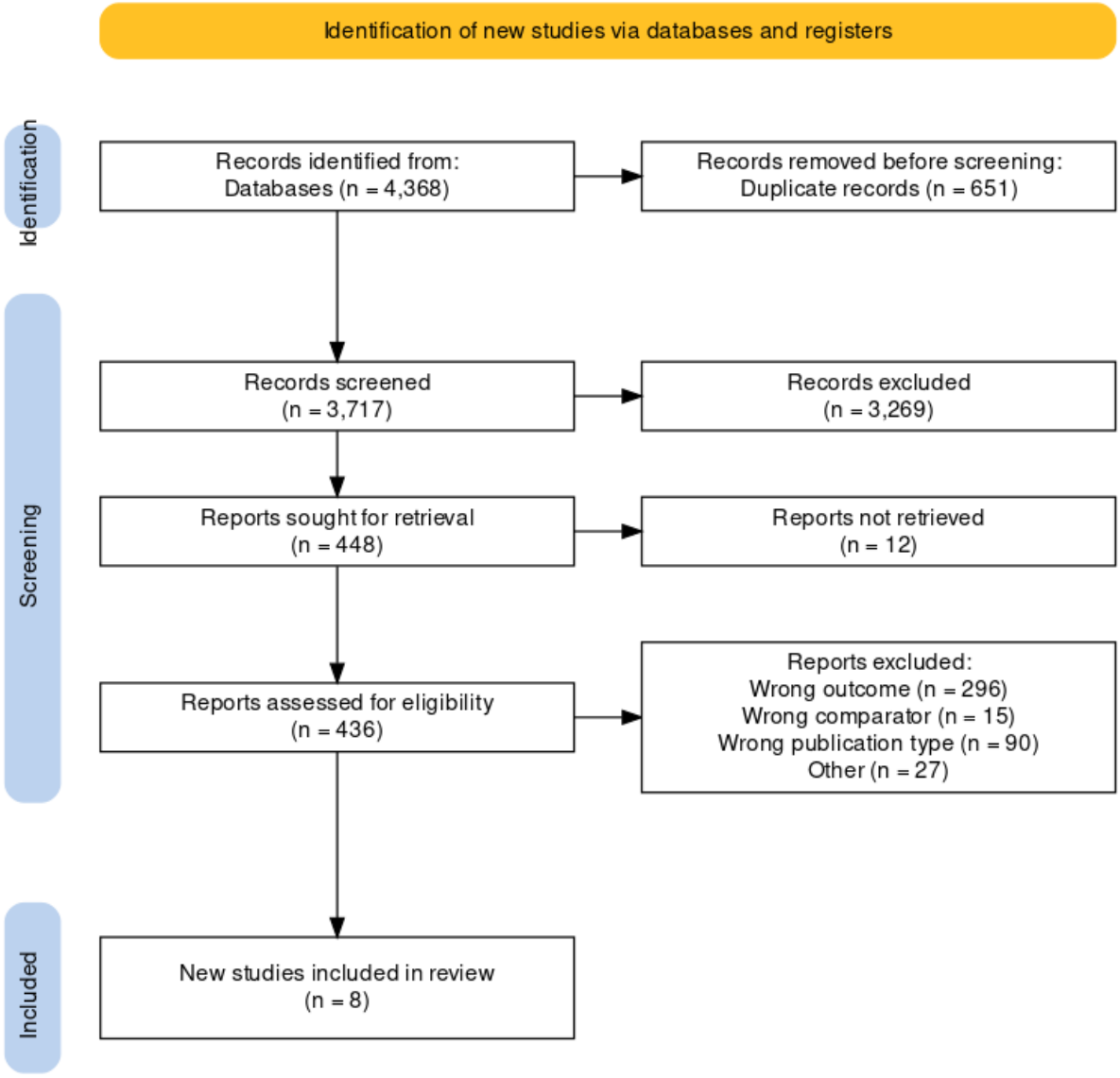

Figure 1 PRISMA flow diagram

Risk of bias

According to the RoB 2.0 tool, both RCTs demonstrated some concerns of bias. According to the ROBINS-I tool, two observational studies demonstrated a moderate risk of bias, two demonstrated a serious risk of bias, and two demonstrated a critical risk of bias. The risk of bias assessments for individual articles is included in Appendix 2.

Study characteristics

Two studies were placebo-controlled randomised controlled trials from the UK. Four of the studies were prospective cohort studies (UK, Netherlands, USA, Pakistan). Two studies were retrospective observational studies from the USA.

Subject characteristics

Table 1 summarises the characteristics of the eight included studies. The number of participants in the studies ranged from 18 to 385. The mean participant age was 63.8, and 64% of the participants were female. The mean BMI was 29.5. The intervention in all studies was an IACI: namely either Methylprednisolone, Triamcinolone, or Dexamethasone. The dose ranged from 10mg of Triamcinolone to 80mg of Methylprednisolone or 6mg of Dexamethasone. This is equivalent to between 1.9mg and 15mg of Dexamethasone. Three of the studies used local anaesthetic in the joint injection in addition to the steroid. Six of the studies investigated IACIs of the knee, one investigated the foot and ankle, and one investigated the hip. The RCTs compared the steroid injection to a placebo of 0.9% saline of the same volume. All studies used a pain scoring system as their main outcome measure. Follow-up ranged from 4 weeks to 1 year.

Table 1 Characteristics of the included studies

Author, Year	Country of Origin	Study Type	Participants (n)	Joint	Intervention	Comparator	Age (mean +/- standard deviation, years)	Age (range, years)	BMI (mean +/- standard deviation)	Sex (M / F)	Key Outcomes	Definition of response to IACI	Predictor Variables	Duration of follow up (months)
Kanthawang, 2020 [15]	USA	ROS	343	Hip	Methylprednisolone or Triamcinolone (plus Ropivacaine)	N/a	59.88 +/- 14.07	NR	27.46 +/- 5.84	134 / 209	VAS, OMERACT-OARSI, binary pain relief, long term pain relief	Immediate: VAS reduction ≥2, or 50% reduction in pain score. Long term: pain resolved at 2-7 months (yes/no)	Age, sex, BMI, baseline pain, steroid type and volume, KL score, OARSI score, DM, dyslipidaemia,	2-7
Jones, 1996 [16]	UK	RCT	60	Knee	40mg Methylprednisolone	IACI 1ml 0.9% saline	70.6	51-89	NR	23 / 37	VAS, EMS	15% reduction in VAS at 3 weeks	Range of movement, fluid, local heat, synovial thickening, tenderness, anxiety score, depression, LHAQ score, quadriceps strength	4
Gaffney, 1995 [17]	UK	RCT	84	Knee	20mg Triamcinolone	IACI 1ml 0.9% saline	67 +/- 9.17	NR	29.71 +/- 15.1	24 / 60	VAS, distance walked in 1 min, health assessment	No set definition	Effusion presence, synovial fluid aspiration, age, duration of symptoms, HAQ,	1-2

											questionnaire, clinical signs of effusion		radiographic severity score, synovial fluid volume and leukocyte count	
Ward, 2008 [18]	UK	POS	18	Foot and ankle	40mg Methylprednisolone	N/a	66.2 +/- 12.8	NR	29.1 +/- 3.6	6 / 12	FAOS	No set definition	Type of arthritis, age, weight, BMI, number of joints injected, laterality, total dose, dose per joint	12
Bevers, 2014 [19]	Netherlands	POS	62	Knee	40mg Triamcinolone	N/a	55.4 +/- 8.7	NR	30.2 +/- 5.6	26 / 36	NRS, USS features, KOOS, analgesic usage	NRS reduction ≥4	Age, gender, BMI, knee swelling at baseline, use of analgesics at baseline, NRS pain, KOOS ADL at baseline, US features	1
Matzkin, 2017 [20]	USA	POS	100	Knee	10mg Triamcinolone (plus Lidocaine)	N/a	61.2 +/- 8.5	44-80	31.2 +/- 7	NR	WOMAC, VNS, SF-36	27.9% reduction or decrease of 1.7 points in VNS 21/7% reduction in WOMAC	Age, height, weight, BMI, smoking status, KL grade, baseline WOMAC, VNS, SF-36	6
Fatimah, 2016 [21]	Pakistan	POS	174	Knee	40mg Methylprednisolone (plus Lignocaine)	N/a	NR	30-80	NR	NR	WOMAC, VAS	>50% improvement in WOMAC score = responders 20-49% improvement = partial responders	Range of movement, local knee tenderness, radiographic score, age, smoking status, hypertension / ischaemic heart disease, DM, BMI, effusion, duration of	3

												>50% improvement in VAS = responders	symptoms, socioeconomic status	
Wu, 2022 [22]	USA	ROS	473	Knee	NR	NR	66.3	NR	29.6	160 / 313	WOMAC	>20% reduction in WOMAC score	Age, BMI, WOMAC pain, stiffness, disability score, analgesic use	1-6

Key:

BMI: Body Mass Index

DM: Diabetes Mellitus

EMS: Early Morning Stiffness

FAOS: Foot and ankle outcome score

KOOS: Knee Osteoarthritis Outcome Score

LHAQ: Lower limb health assessment questionnaire

NR: Not reported

NRS: Numerated Rating Scale (0-10)

OARSI: Osteoarthritis Research Society International

OMERACT: Outcome Measures for Arthritis Clinical Trials

POS: Prospective Observational Study

RCT: Randomised Controlled Trial

ROM: Range of Movement

ROS: Retrospective Observational Study

SF-36: Medical Outcomes Study 36-item Short Form

USS: Ultrasound Scan

VAS: Visual Analogue Scale

VNS: Visual Numeric Scale

WOMAC: Western Ontario and McMaster Universities Arthritis Inde

The overall response to IACIs

Each study used different definitions of response to IACIs. For example, Fatimah et al. used 50% or more improvement in VAS or WOMAC score at 3 months whereas Bevers et al. used NRS ≤4 at 4 weeks. These are detailed in Table 1. Therefore, there was significant variation in the quantification of pain responses among the included studies.

Kanthawang et al. showed an 85.3% improvement in VAS and 79.8% improvement in OMERACT-OARSI at 15 minutes post-injection and 32.7% improvement at >2 months. Ward et al. showed maximal improvement at 4 weeks after which response deteriorated up to 6 months. Bevers et al. showed 42% of patients achieved pain response at 4 weeks (NRS ≤4). Fatimah et al. showed 16.1% had 50% of more improvement in WOMAC score at 3 months post IASI and 38.7% had 50% or more improvement in VAS score. Matzkin et al. found pain relief at all time points up to 6 months according to the WOMAC scale. Gaffney et al. reported 78% had overall improvement at 1 week and 57% at 6 weeks. Jones et al. showed a 93% positive response in VAS criteria at 3 weeks. Wu et al. showed 67% of participants had a reduction in WOMAC score of >20%.

Predictors of Response to IACIs

Baseline pain

Kanthawang et al. found that baseline pain positively correlated with immediate pain response to IACI ($p<0.001$) using VAS, but this was not demonstrated with the OMERACT-

OARSI measure. Jones et al. found that joint tenderness was associated with a positive response to IACI when crude odds ratios were considered. Wu et al. found that a higher baseline WOMAC pain score was significantly associated with a positive response ($p<0.001$). This was also linked with baseline disability scores ($p=0.002$) and stiffness scores ($p=0.015$). Bevers et al. reported that more frequent baseline analgesic use (an indirect indicator of higher baseline pain) was associated with a positive response to IACI ($p=0.01$). However, Fatimah et al. reported that joint tenderness showed a negative correlation with response to IACI ($p=0.04$), and Gaffney et al. found no correlation between baseline pain and response to IACI.

Age

Kanthawang et al. showed that older age correlated with longer-term pain relief from IACI ($p=0.01$). However, Fatimah et al. reported that age was negatively correlated with response ($p=0.025$) and Wu et al. found no difference.

BMI

Kanthawang et al. found that patients with higher BMI had more immediate pain relief when assessing pain relief using change in VAS ($p=0.01$). However, this was not replicated with the OMERACT-OARSI scale. Matzkin et al., Wu et al., and Fatimah et al. reported no correlation between BMI and response to IACI.

Range of movement

Fatimah et al. found that a low range of movement showed a negative correlation with response to IACIs ($p=0.01$).

Joint effusion

Gaffney et al. demonstrated greater improvement in VAS in patients with clinically evident joint effusion ($p<0.05$) and patients who had synovial fluid aspirated at the time of injection ($p<0.01$). However, Jones et al. and Fatimah et al. did not find this to be a significant prediction of patient response.

Radiography

Three studies assessed radiographic scores at baseline using the Kellgren-Lawrence (KL) scoring system. Kanthawang et al. showed a higher incidence of immediate pain relief after IACI in the hip if the pre-injection KL score was higher ($p=0.03$). Their study also demonstrated that femoral osteophytes, inferior acetabular osteophytes, superior joint space narrowing, and central joint space narrowing correlated with immediate pain relief ($p=0.03$, 0.01, 0.02, 0.03 respectively). However, only the presence of inferior acetabular osteophytes remained significant for long-term pain relief after adjusting for age and BMI ($p=0.1$).

Conversely, in the knee, Matzkin et al. demonstrated that patients with more severe radiographic osteoarthritis experienced less pain relief and functional improvement. Fatimah et al. also reported a negative predictive correlation with higher radiographic scores, indicating a poorer response to steroid injection ($p=0.0$). Gaffney et al. did not find any significant difference in radiographic features.

Ultrasound (US) features

Bevers et al. found that infrapatellar bursitis was suggestive of increased efficacy of IACI in the knee. It is important to note this is a rare finding based on a sample of 6 patients, presenting the possibility of a spurious finding.

All other factors reviewed in the eight studies including sex, smoking, mental health status, hypertension/ischaemic heart disease, diabetes mellitus, duration of symptoms, and socioeconomic status did not demonstrate any correlation with the prediction of positive or negative outcomes after IACIs.

Discussion

Our systematic review identified eight studies which have attempted to investigate a variety of factors that may predict the response to IACIs. Features including higher baseline pain, older age, higher BMI, lower range of movement, higher Kellgren-Lawrence radiographic score, joint effusion and aspiration have been identified as predictors of positive outcomes following the use of IACI. However, these findings are inconsistent and variable. Due to the heterogeneity of outcomes, variables and quality between the studies, it was not possible to pool the results or perform a formal meta-analysis; therefore, a narrative review of the findings has been provided.

Thus far, only one systematic review of predictors of response to IACIs in knee osteoarthritis has been performed by Maricar et al. in 2013 [15]. This previous study identified that the presence of joint effusion, aspiration of synovial fluid, disease severity, US-guided injection, and more symptomatic baseline disease may be positive predictors of response. Similar to our review, due to the heterogeneity of findings, only a narrative review of findings was provided.

The predictor with the most evidence was baseline pain, with four studies supporting higher baseline pain as a positive predictor of response to IACI. This also seemed to be consistent across the numerous measurement scales (VAS, WOMAC, and NRS). It should be remembered that osteoarthritis is a multifactorial disease with heterogenous phenotypes in terms of its underlying pathology. Consequently, the anti-inflammatory effects of IACIs may be most pronounced in patients with higher degrees of inflammatory features, which are

detected clinically as higher baseline pain, as is seen in higher rates of joint effusions, and bursitis. However, in some subgroups, where pain is not solely inflammatory but also due to structural, mechanical, or extra-articular factors, the use of IACI may offer brief or no therapeutic benefit. This theory is supported in Maricar's review which demonstrated that the presence of effusion, worse pain, stiffness, and function were positive predictors of response to IACIs.

However, Gaffney et al. did not find any correlation and Fatimah et al. even showed a negative correlation with baseline pain despite using WOMAC and VAS as the main outcome measures. Maricar's review also found that synovitis, thought to be a sign of inflammation, was not a positive predictive factor. This highlights the inconsistency of the findings across the reports, despite using consistent outcome measures. One explanation for this may be utilising differing responder criteria. As seen in Table 1, despite using the same outcome measures, each report used different definitions of response. Previous research has been published detailing proposals of responder criteria for clinical trials in osteoarthritis, including a >20% reduction in WOMAC pain score [16]. However, despite this being published in 2004, only one of the studies included in this review utilised this (Wu et al.) This must be utilised in further studies to allow true comparison or a core outcome set including adequate patient representation developed.

The link between BMI and a positive pain response after IACI may be a false correlation. A previous study found that patients with higher BMI had higher baseline pain [17]. This is echoed by a study included in this systematic review. Matzkin et al. showed that obese patients (BMI >30) had worse WOMAC scores at every time point post-IACI when compared

with non-obese participants. Yet, a meta-analysis performed by Middelkoop et al. showed that higher baseline pain was associated with more short-term pain relief following IACI [18]. This is supported by Kanthawang et al. and Wu et al. who found that higher baseline pain positively correlated with immediate pain response after IACI. It may be that instead of high BMI being a positive predictive factor, higher baseline pain is the true positive predictive factor, and patients with high BMI tend to have higher baseline pain – however, no study assessed this.

Immediate pain relief identified in several reports may be confounded by the simultaneous inclusion of local anaesthetic in injections. This may explain why Kanthawang et al. found that the presence of immediate pain relief did not correlate with the presence of long-term pain relief since even long-acting local anaesthetics can only provide analgesia for 4-18 hours. However, Ward et al. did show that an improvement at 4 weeks and 3 months post-IACI correlated with a prolonged course of improvement to 9 months and 1 year (their study utilised Methylprednisolone only).

The significance of joint aspiration before IACI may not be related to an increased response to IACI but, rather, a proven injection into the correct intra-articular space. A study by Jones et al. showed that 34% of knee injections were either extra-articular or in uncertain locations [19]. If the synovial fluid is aspirated, you can be relatively confident that your steroid injection will be intra-articular. Maricar's review also studied sonographically-guided injections, and found that whilst there was initially an improved therapeutic effect, pain outcomes at six months were similar, whether the injection had been performed based on anatomical landmarks or sonographically-guided. Only two studies in our review were

image-guided: Ward and Kathawang. Although these two studies both showed positive effects of IACIs, they were not randomised controlled trials, like the study referenced in Maricar's review. Additionally, these two studies are the only two in our review that did not assess the effects of IACIs for knee osteoarthritis, and as such it would be inappropriate to make comparisons. This was also beyond the scope of review.

This study does have limitations which must be considered. Firstly, each of the included studies used different criteria to assess response to IACI and different time frames for assessment and follow-up. Inter-study comparisons are therefore challenging. Moreover, several of the studies that used two criteria to assess response to IACIs themselves noticed differences in results across various assessment and scoring criteria within the same patient cohort. Secondly, there was significant variation in the formulation and dose of steroid used, as well as whether local anaesthetic was additionally used. Even if this had been controlled throughout the studies, it would still have been challenging to inject the same dose each time as individual patients' tolerances may potentially limit the volumes injected or some injected into soft tissue. Thirdly, the included studies covered a range of joints including hips, knees, ankles, and feet. Predictors may not be able to be generalised across these. Of note, Ward et al.'s study of ankles and feet did not find any positive or negative predictors of response to IACIs. Finally, the quality and risk of bias within the included studies were variable: some studies had very small patient cohorts, some had female-only cohorts only, and some had high patient attrition rates.

Further research is essential to conduct a comprehensive investigation of the initial findings from these studies. Achieving a homogenised approach regarding injection technique,

steroid dosage, local anaesthetic usage, and standardisation of outcome measurement and frequency is crucial for accurate comparisons. To ensure unbiased and precise assessments, absence of local anaesthesia and consistent steroid form and dose (e.g., 40mg Methylprednisolone) could be used. Standardising outcome measurements is equally important, and would facilitate meta-analysis to assist the determination of the reliability and significance of predictive factors for the response to IACIs. The utilisation of a core set of outcome measures such as those outlined by OMERACT-OARSI for clinical trials of hip and/or knee osteoarthritis should be routinely implemented [20]. Additionally, routine assessment of ultrasound features and the Kellgren-Lawrence score should be recorded, as these are cheap and accessible investigations. Ideally, the duration of follow-up should extend beyond 6 months.

Conclusion

This review has identified inconsistent and variable findings across the existing literature. Despite this, features including higher baseline pain, older age, higher BMI, lower range of movement, higher Kellgren-Lawrence radiographic score, joint effusion and aspiration have been identified as predictors of positive outcomes following the use of IACI – albeit, the evidence was of mixed quality. Further research with standardisation of IACI administration and outcome measures is required to facilitate further analysis of the reliability and significance of predictive factors for IACI in patients with OA.

Author Contributions:

RLD designed the study. FES and RLD performed data collection analysis and interpretation. FES wrote the first draft of the manuscript. All authors interpreted data and drafted and reviewed the final manuscript. All authors approved the submitted manuscript.

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All contributors met criteria for authorship.

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Competing interest statement:

VW and MRW disclose financial activities, all outside the submitted work.

Ethics approval:

Not applicable

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Appendix 1 – Example of Detailed Search Strategy (Medline version)

Database: Ovid MEDLINE(R) <1946 to present>

Search Strategy:

1 adult*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (6448632)

2 exp Adult/ (7943654)

3 1 or 2 (8661728)

4 (osteoarthriti* or osteo-arthriti* or joint arthriti* or bon* arthriti* or arthriti*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (340926)

5 exp Osteoarthritis/ (77253)

6 4 or 5 (340926)

7 exp Injections, Intra-Articular/ (9317)

8 (inject* or joint inject* or arthrocentes* or intraarticul* or intra-articul* or intra* articul*).mp. [mp=title,

book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (998098)

9 7 or 8 (998138)

10 (steroid* or corticosteroid* or cortico-steroid* or cortico* or glucocortico* or methylpred* or methyl-pred* or methyl* pred* or triamcinolon*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (660203)

11 exp Glucocorticoids/ (207253)

12 exp Prednisolone/ (53863)

13 exp Steroids/ (921417)

14 exp Adrenal Cortex Hormones/ (424283)

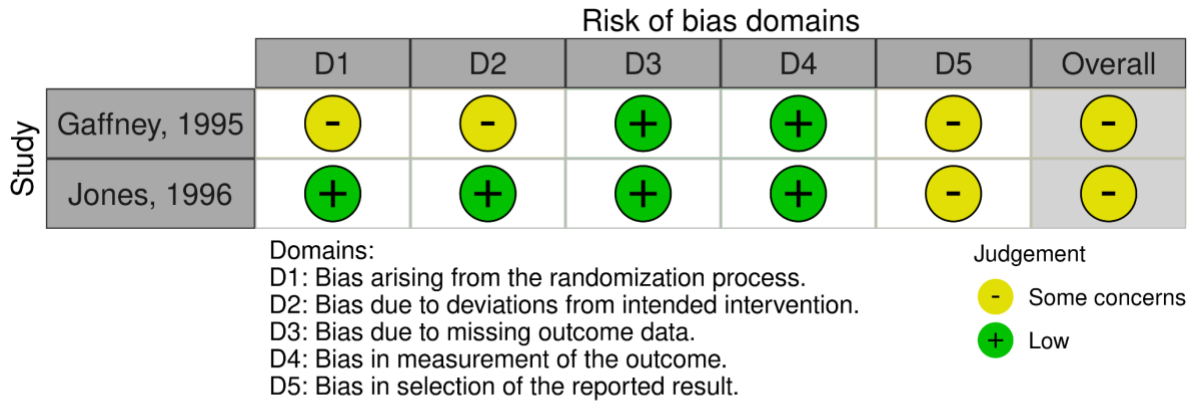
15 10 or 11 or 12 or 13 or 14 (1359870)

16 3 and 6 and 9 and 15 (2039)

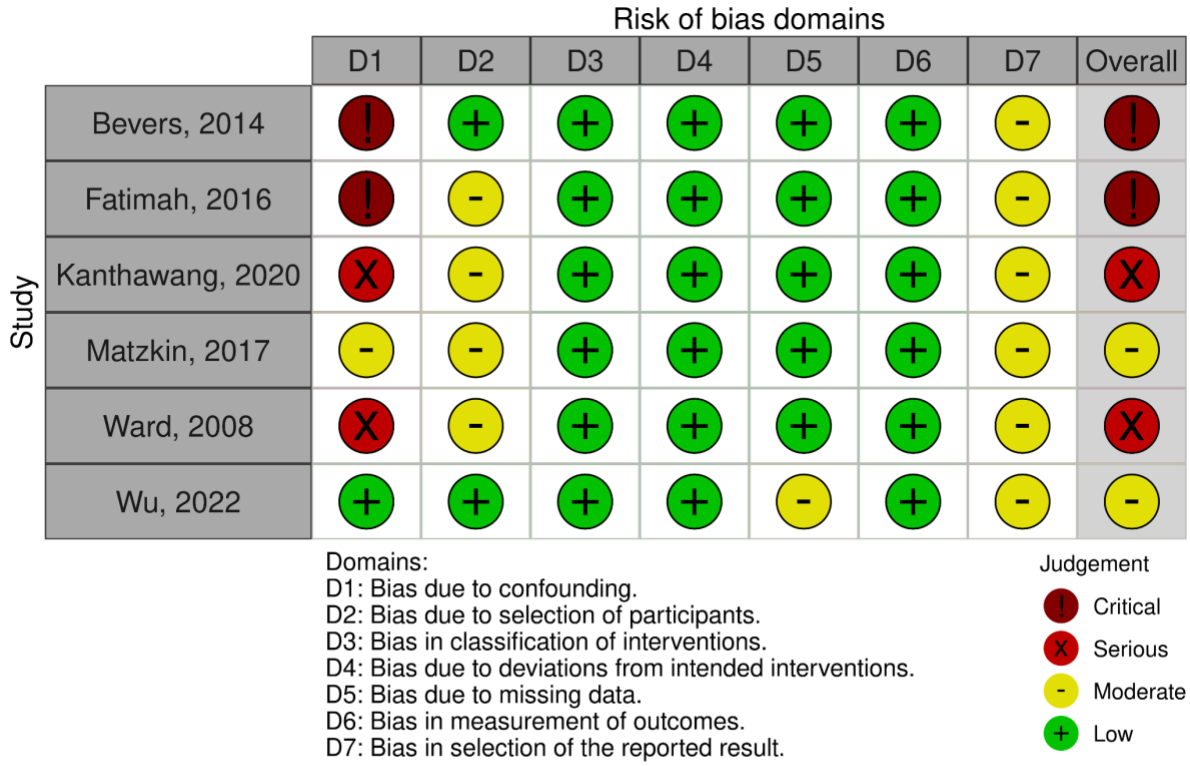
17 limit 16 to (english language and yr="2021 - 2024") (152)

Appendix 2 – Risk of Bias Assessments

Interventional studies – RoB tool



Observational studies – ROBINS-I too



Data collection forms, extracted data, and analyses all available on request.