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Osteoarthritis and Cartilage

Effects of recurrent intra-articular corticosteroid injections for osteoarthritis at 3 months and beyond: a systematic review and meta-analysis in comparison to other injectables

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SUMMARY

Objective: Intra-articular corticosteroid injections (IACIs) provide temporary symptom relief in osteoarthritis (OA). This meta-analysis investigated the effects of recurrent IACIs at 3 months and beyond.
Design: We searched Medline, Embase and Cochrane from inception to January 2021 for randomised controlled trials (RCTs) of patients with OA who received recurrent IACIs compared with other injectables, placebo or no treatment (primary outcomes: pain, function). Mean differences (MDs) with 95% confidence intervals were reported.
Results: Ten RCTs were included (eight knee OA (n = 763), two trapeziometacarpal OA (n = 121)). Patients received between 2 and 8 injections, varying by trial. Trials compared recurrent IACIs with hyaluronic acid (HA), platelet-rich plasma (PRP), saline or orgotein (follow-up 3–24 months). Greater improvements in pain, function and QoL at 3–24 months were noted for the comparators than with IACIs, with comparators demonstrating an equal or superior effect, or the intervention effect attenuated during follow-up. Recurrent IACIs demonstrated no benefits in pain or function over placebo at 12–24 months. No serious adverse events were recorded. No studies reported on time-to-future interventions, risk of future prosthetic joint infection or other adverse events associated with subsequent joint replacement.
Conclusions: Recurrent IACIs often provide inferior (or non-superior) symptom relief compared with other injectables (including placebo) at 3 months and beyond. Other injectables (HA, PRP) often yielded greater improvements in pain and function up to 24 months post-injection. Existing RCTs on recurrent IACIs lack sufficient follow-up data to assess disease progression and time-to-future interventions.

Introduction

Intra-articular corticosteroid injections (IACIs) are a well-established non-surgical treatment option for the symptoms of osteoarthritis (OA), which can provide short-term improvements in pain, disability and quality of life (QoL)[1]. The benefits tend to be greater for those with advanced disease[2]. IACIs have been used for decades, most commonly for knee OA. Given the progressive nature of OA, a proportion of these patients will later require more invasive surgical interventions. IACIs are a relatively safe non-surgical means of temporary relief of symptoms - they can be a key

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treatment component for patients who are not fit for surgical interventions, for those where there is diagnostic uncertainty, or for those whose current symptoms are not severe enough for them to consider undergoing joint replacement.

Numerous alternative injectables exist including anti-inflammatories, botulinum toxin, hyaluronic acid (HA), platelet-rich plasma (PRP) and, more recently, stem cells and biologics[3]. All of these have been demonstrated to provide symptomatic relief in the short term, but there is often significant heterogeneity between trials[4]. Moreover, there is a strong placebo effect which may contribute to the difficulty in detecting differences between treatment groups in trials[5–7].

Many contemporary studies, reviews and meta-analyses reach contrasting conclusions regarding which intra-articular injectable is superior for patients with knee OA[8–14] and hip OA[15], often having assessed different outcomes over variable periods, and focussing on single-dose injections. Similarly, a recent meta-analysis of a variety of injectables to treat patients with trapeziometacarpal OA demonstrated a mild improvement in pain with IACIs vs HA, but the strength of the recommendation was limited, and neither was considered to be superior overall[16]. Another meta-analysis for this group demonstrated that IACIs were more effective at reducing pain at 24 months, but HA was more effective at improving function over the same period[17]. Again, most of the existing trials have focussed on outcomes after single-dose injections.

Outcomes for recurrent IACIs at 3 months and beyond remain less well-researched[4]. This systematic review and meta-analysis aimed to assess the existing literature to investigate the effects of recurrent IACIs at 3 months and beyond when compared to other injectables, placebo or no treatment.

Materials and methods

Data sources and search strategy

The review was registered *a priori* in the PROSPERO prospective register of systematic reviews (ID: CRD42020226861) and conducted according to a predefined protocol and in line with PRISMA guidelines. We searched for randomised controlled trials (RCTs) which compared longer-term outcomes (at 3 months post-injection and beyond) after recurrent IACIs were used to treat OA compared with other common injectables (e.g., botulinum toxin, HA, PRP), placebo (e.g., saline), sham treatment or no treatment. We systematically searched the databases of Medline, Embase and Cochrane from inception to 07 January 2021. 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., "corticosteroid," "methylprednisolone"). There were no restrictions on 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. The detailed search strategy has been provided in Appendix 1.

Eligibility criteria

We included RCTs that reported on longer-term outcomes at 3 months post-injection and beyond after recurrent ($\geq$ two injections in the study period) IACIs in adults (age >18 years) for OA compared with other common injectables, placebo, sham treatment or no treatment. The primary outcome was patient-reported outcome measures (PROMs) including pain and function. Secondary outcomes of interest included QoL, joint stiffness, adverse events (e.g., infection, cardiovascular events), disease progression, and time-to-future interventions (e.g., arthroscopy, arthroplasty).

We excluded any studies that only assessed outcomes after single-dose injections, studies that included patients with prosthetic joints, and patients with pathology other than OA (e.g., rheumatoid arthritis, gout). Non-RCTs were also excluded.

Study selection and data extraction

Once the searches were completed, the results were imported into Rayyan[18], 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, TAE) against predefined eligibility criteria. Any discrepancies regarding the eligibility of an article were discussed, and a consensus was achieved through a senior author (MRW) if required. One reviewer (RLD) independently extracted data and conducted risk of bias assessments using a standardised data collection form. A second reviewer (TAE) 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, geographical location, study design, number of participants, mean age, percentage of males, joint treated (e.g., knee), intervention (corticosteroid (CS)), comparators, indications, duration of follow-up, and outcome measures. 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. Authors of eligible studies were contacted to provide further information if there were missing data for the extracted fields.

Risk of bias assessment

The risk of bias within individual RCTs was assessed using the Cochrane Risk of Bias (RoB 2.0) tool[19], a validated tool for assessing the risk of bias of 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.

Statistical analysis

A meta-analysis was performed using RevMan 5.4 software (Cochrane Collaboration). Summary measures were presented as mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes and relative risks (RRs) with 95% CIs for binary outcomes. Standardised mean differences (SMDs) were employed if studies used different scales of measurement. For continuous data, if the mean or standard deviation (SD) was not reported, we estimated the mean and variance from the reported median, range, and sample size as recommended by Hozo *et al.*[20], to facilitate a consistent approach to the meta-analysis. For continuous data that only reported the mean and 95% CIs, the SD was calculated as per instructions in the Cochrane Handbook (Chapter 7.7.3.2)[21]. Relative risks were calculated from the extracted raw counts for the intervention and comparator. We combined comparators (non-CS) for the analysis. A narrative synthesis was performed for studies that could not be pooled. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. The inverse variance (IV) weighted method was used to combine pooled summary measures. Parallel analyses used fixed-effects (FE) models. The decision to use random-effects (RE) or FE models was

based on I^2 quantification of heterogeneity, as well as variability in the clinical and methodological aspects of the studies, number of studies available for pooling, and study sample sizes[22,23]. The statistical significance was set as $p < 0.05$. We planned to conduct subgroup analysis to explore the origins of heterogeneity using random-effects meta-regression.

Results

Study selection

Our search strategy identified 593 potentially relevant citations, and this was reduced to 439 after duplicates were removed. After the initial screening of titles and abstracts, 119 full-text articles remained for further evaluation, and a further one was obtained by manually scanning the reference lists of the retrieved articles. 110 papers failed to meet the eligibility criteria. Therefore, ten studies that contained extractable data were deemed eligible for inclusion in this systematic review and meta-analysis[24–33]. A PRISMA flow chart is provided in Fig. 1.

Study characteristics

Table I provides a summary of the characteristics of the ten included RCTs. Eight studies assessed injections into knee joints ($n = 763$), and two studies assessed injections into trapeziometacarpal joints ($n = 121$). Six studies were performed in Europe (Germany, Greece, Italy, Spain, Sweden, Turkey), three in North America (USA, Canada, Mexico), and one in the Middle East (Iran). Regarding recurrent injections for knee OA, four studies

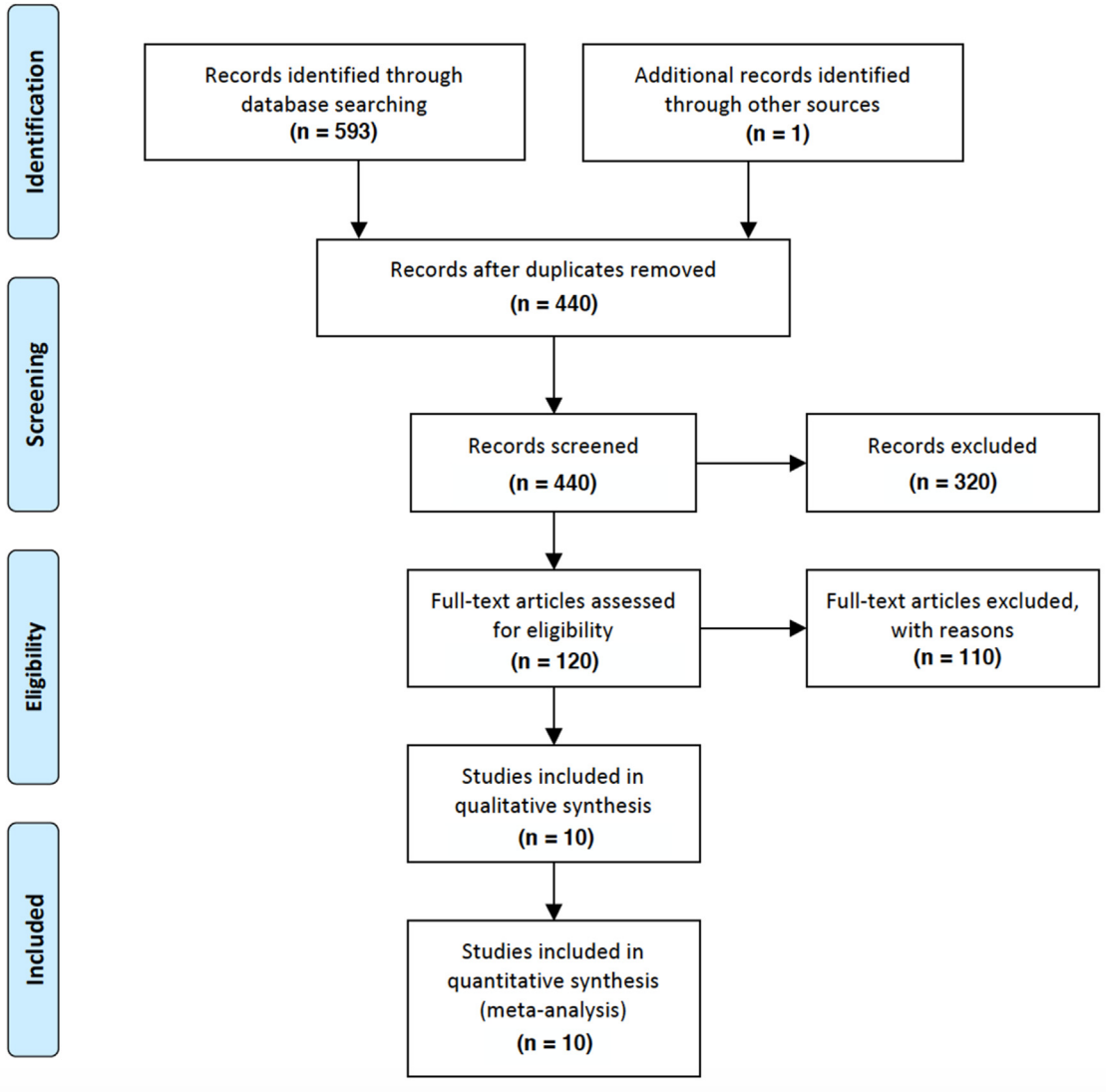

Fig. 1

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PRISMA flow chart.

Author Year *Location*	Study Design	Participants (n)	Joint	Intervention (corticosteroid)	Comparator	Age (years) Mean ± SD (range)	Sex (male, %)	Main Outcomes	Maximum Follow-Up (months)
Bisicchia 2016 *Italy*	Single-centre single-blinded prospective RCT	150	Knee	MP 40 mg 2 injections 1 week apart	HA 2 injections 1 week apart	MP: 68.6 ± 9.9 (54–80) HA: 71.5 ± 10.6 (48–84)	MP: 33.3 HA: 29.3	WOMAC, VAS, SF-36	12
Davalillo 2015 *Mexico*	Single-centre single-blinded prospective RCT	200	Knee	BM 7 mg 2 injections 4 weeks apart	HA 5 injections 1 week apart	BM: 62.8 ± 0.6 HA: 62.7 ± 0.6	BM: 41.8 HA: 39.2	VAS, WOMAC	12
Gammer 1984 *Sweden*	Single-centre double-blinded prospective RCT	36	Knee	MP 40 mg 4 injections Weeks 1/2/4/6	Orgotein 8 mg 4 injections Weeks 1/2/4/6	Overall: 63 (48–72)	NR	Stiffness, VAS, adverse events	6
Malahias 2018 *Greece*	Mutli-centre single-blinded prospective RCT	33	Trapezio-metacarpal	MP 125 mg + LA 2 injections 2 weeks apart	PRP 2 injections 2 weeks apart	MP: 63 ± 11.8 PRP: 62.8 ± 10.6	MP: 19 PRP: 19	VAS, Q-DASH, patient satisfaction	12
McAlindon 2017 *USA*	Single-centre double-blinded prospective RCT	140	Knee	TA 40 mg 8 injections 3 months apart	Saline 0.9% 1 mL 8 injections 3 months apart	TA: 59.1 ± 8.3 Saline: 57.2 ± 7.6	TA: 47.1 Saline: 45.7	ROM, BP, WOMAC, VAS, adverse events, function, SF-36	24
Monfort 2015 *Spain*	Single-centre single-blinded prospective RCT	88	Trapezio-metacarpal	BM 3 mg 3 injections 1 week apart	HA 3 injections 1 week apart	Overall: 62.8 ± 8.7 (45–92)	Overall: 12.5	VAS, FIHOA, SF-36	6
Nabi 2018 *Iran*	Single-centre single-blinded prospective RCT	67	Knee	TA 40 mg 3 injections 4 weeks apart	PRP 3 injections 4 weeks apart	TA: 58.6 ± 8.8 PRP: 59.1 ± 7.8	TA: 20.6 PRP: 15.2	VAS, KOOS	6
Raynauld 2003 *Canada*	Single-centre double-blinded prospective RCT	68	Knee	TA 40 mg 8 injections 3 months apart	Saline 0.9% 1 mL 8 injections 3 months apart	TA: 63.1 ± 9.1 Saline: 63.3 ± 9.0	TA: 26 Saline: 39	WOMAC, VAS, ROM, adverse events	24
Skwara 2009 *Germany*	Single-centre single-blinded prospective RCT	42	Knee	TA 10 mg 5 injections 1 week apart	HA 5 injections 1 week apart	TA: 61.3 ± 6.7 HA: 60.8 ± 7.0	TA: 42.9 HA: 38.1	KSS, Lequesne, VAS	3
Tascioglu 2003 *Turkey*	Single-centre single-blinded prospective RCT	60	Knee	MP 40 mg 3 injections 1 week apart	HA 3 injections 1 week apart	MP: 60.1 ± 6.9 HA: 57.4 ± 6.5	MP: 0 HA: 0	VAS, Lequesne, ROM, adverse events	6

Key (alphabetical): BM, betamethasone; BP, blood pressure; FIHOA, functional index of hand osteoarthritis; HA, hyaluronic acid; KOOS, knee injury and osteoarthritis outcome score; KSS, knee society score; LA, local anaesthetic; MP, methylprednisolone; NR, not reported; PRP, platelet-rich plasma; Q-DASH, disabilities of the arm, shoulder and hand questionnaire; ROM, range of motion; SF-36, 36-item short-form survey; TA, triamcinolone; VAS, visual analogue scale; WOMAC, western Ontario and McMaster universities arthritis index.

Table I

Characteristics of the included studies

Osteoarthritis and Cartilage

compared CS with HA[24,25,32,33], two with saline (placebo)[28,31], one with PRP[30], and one with an anti-inflammatory agent (orgotein)[26]. Regarding recurrent injections for trapeziometacarpal OA, one study compared CS with HA[29] and one with PRP[27]. Most patients included in the studies were female, and the mean age was in the fifth or sixth decade of life. The maximum follow-up duration was 24 months (range 6–24 months), and no study reported a mean or median follow-up duration.

Risk of bias

According to the RoB 2.0 tool, nine RCTs were deemed to be of low risk of bias, and one was deemed to have some concerns. The risk of bias assessment for individual articles is included in Appendix 2.

Knee OA

CS vs 'other' in patients with knee OA[24–26,28,30–33]

Pain

All eight studies assessed pain using the Visual Analogue Scale (VAS) pain scores (scale 0–10 or 0–100, where the lower limit represents no pain and the upper limit represents extreme pain). At 3 months, there was no difference in VAS (SMD 0.33; 95% CI −0.44, 1.10; $p = 0.40$; Fig. 2(A)). Greater improvements in VAS were noted in the 'other' group at 6 months (SMD 1.05; 95% CI 0.54, 1.56; $p < 0.0001$; Fig. 2(B)) and 9 months (SMD 2.06; 95% CI 1.71, 2.40; $p < 0.00001$; Fig. 2(C)). However, there was no difference between treatment groups at 12 months (SMD 0.83; 95% CI −0.58, 2.24; $p = 0.25$; Fig. 2(D)) nor 24 months (SMD −0.01; 95% CI −0.30, 0.28; $p = 0.94$; Fig. 2(E)).

Function

Davalillo *et al.*, McAlindon *et al.* and Raynauld *et al.* assessed function using the WOMAC function scale (scale 0–68, where the lower limit represents no disability and the upper limit represents extreme disability), and Skwara *et al.* and Tascioglu *et al.* used the Lequesne functional index to assess function (scale 0–24, where the lower limit represents no disability and the upper limit represents extreme disability). At 3 months, function scores had improved in both groups but greater improvements in function were noted in the 'other' group (SMD 0.82; 95% CI 0.19, 1.45; $p = 0.01$; Fig. 3(A)). This trend continued at 6 months (SMD 1.98; 95% CI 1.66, 2.30; $p < 0.00001$; Fig. 3(B)), 9 months (SMD 3.52; 95% CI 3.07, 3.97; $p < 0.00001$; Fig. 3(C)) and 12 months (SMD 1.61; 95% CI 1.30, 1.93; $p < 0.00001$; Fig. 3(D)). At 24 months, there was no difference between treatment groups (SMD −0.10; 95% CI −0.39, 0.19; $p = 0.51$; Fig. 3(E)).

Nabi *et al.* measured function using the KOOS activities of daily living (ADLs) scale (scale 0–100, where the lower limit represents extreme disability and the upper limit represents no disability). Improvements in scores were seen in both treatment groups, but greater improvements in scores were noted in the 'other' group at 3 months (MD −8.02; 95% CI −11.24, −4.80; $p < 0.00001$; Fig. 4(A)) and 6 months (MD −18.55; 95% CI −21.81, −15.29; $p < 0.00001$; Fig. 4(B)).

QoL

Bisicchia *et al.* quantified QoL using the 36-Item Short Form Survey (SF-36) score (scale 0–100, where the lower limit represents extreme disability and the upper limit represents no disability). Greater improvements in QoL were noted in the 'other' group at 3 months (MD −8.00; 95% CI −12.61, −3.39; $p = 0.0007$; Supplementary Material Fig. A) and 6 months (MD −11.40; 95% CI −15.64, −7.16; $p < 0.00001$; Supplementary Material Fig. B). At 12 months, the 'other' group had returned to baseline and a small improvement in the CS group was maintained (MD −2.70; 95% CI −7.10, 1.70; $p = 0.23$; Supplementary Material Fig. C).

Nabi *et al.* assessed QoL using the KOOS QoL scale (scale 0–100, where the lower limit represents extreme impact on QoL and the upper limit represents no effect of QoL). Improvements in KOOS scores were seen in both treatment groups, but greater improvements in QoL were noted in the 'other' group at 3 months (MD −6.35; 95% CI −11.70, −1.00; $p = 0.02$; Supplementary Material Fig. D) and 6 months (MD −10.26; 95% CI −15.30, −5.22; $p < 0.0001$; Supplementary Material Fig. E).

Trapeziometacarpal OA

CS vs 'other' in patients with trapeziometacarpal OA[27,29]

Pain

Malahias *et al.* and Monfort *et al.* assessed VAS pain scores (scale 0–10 or 0–100). Although both treatments led to improvements in pain, there was no difference in VAS between treatment groups at 3 months (SMD −0.11; 95% CI −0.47, 0.26; $p = 0.57$; Fig. 5(A)) or 6 months (SMD 0.95; 95% CI −0.06, 0.79; $p = 0.09$; Fig. 5(B)). However, at 12 months, greater improvements in VAS were noted in the 'other' treatment group (SMD 3.95; 95% CI 2.71, 5.20; $p < 0.00001$; Fig. 5(C)).

Function

Malahias *et al.* evaluated function using the Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH) score (0–100, where the lower limit represents no disability and the upper limit represents extreme disability) and Monfort *et al.* used the Functional Index of Hand Osteoarthritis (FIHOA) score (scale 0–30, where the lower limit represents no disability and the upper limit represents extreme disability). Improvements in functional scores were seen in both treatment groups, but greater improvements in function were noted in the 'other' group at 3 months (SMD 0.80; 95% CI 0.42, 1.18; $p < 0.0001$; Fig. 6(A)), 6 months (SMD 0.82; 95% CI 0.38, 1.26; $p = 0.0002$; Fig. 6(B)), and 12 months (SMD 0.80; 95% CI 0.07, 1.52; $p = 0.03$; Fig. 6(C)).

QoL

Monfort *et al.* evaluated QoL using the SF-36 physical score (scale 0–100). Although both treatments led to improvements in QoL, there was no difference in scores between treatment groups at 3 months (MD −0.01; 95% CI −3.52, 3.50; $p = 1.00$; Supplementary Material Fig. F) and 6 months (MD 1.77; 95% CI -2.22, 5.76; $p = 0.38$; Supplementary Material Fig. G).

Adverse events

Adverse events were uncommon in all treatment groups for patients with knee OA and trapeziometacarpal OA. Some patients experienced mild symptoms of pain/discomfort, swelling, stiffness, pruritis or erythema but these were short-lived and self-resolving after hours/days. No severe adverse events or complications were reported across the ten studies.

Subgroup analysis

CS vs HA in patients with knee OA[24,25,32,33]

Pain

All four studies assessed pain using VAS pain scores (scale 0–10 or 0–100). At 3 months, there was no difference in VAS (SMD 0.23; 95% CI −0.85, 1.31; $p = 0.68$). At 6 months (SMD 1.03; 95% CI 0.25,

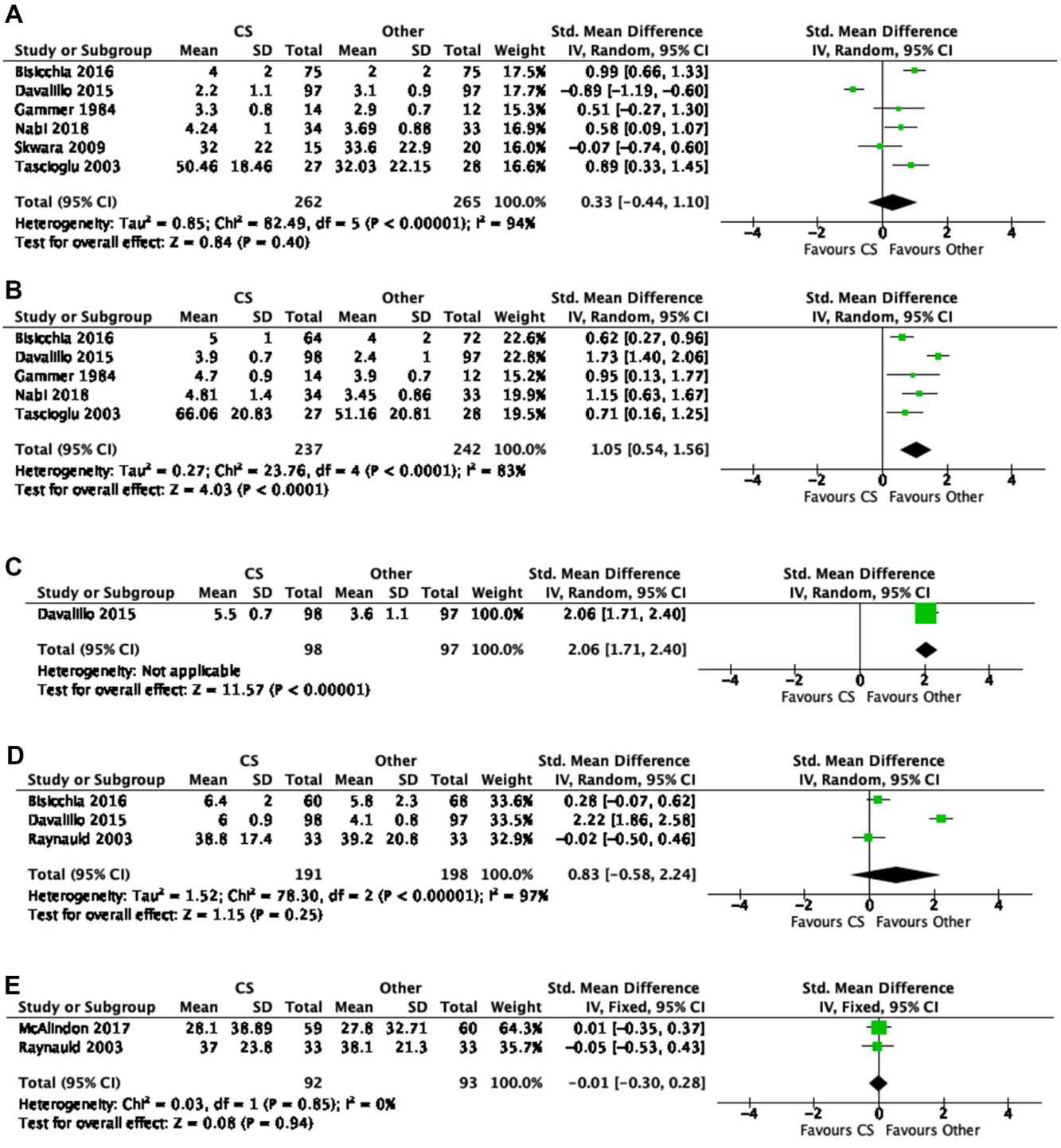

Fig. 2

Osteoarthritis and Cartilage

Forest plots demonstrating differences in VAS pain scores for CS vs 'other' in patients with knee OA at 3 months (2A), 6 months (2B), 9 months (2C), 12 months (2D) and 24 months (2E).

1.81; $p = 0.01$), 9 months (MD 1.9; 95% CI 1.64, 2.16; $p < 0.00001$) and 12 months (MD 1.78; 95% CI 1.55, 2.01; $p < 0.00001$) VAS was lower in the HA group.

Function

Davalillo *et al.* assessed function using the WOMAC function scale (scale 0–68). At 3 months, WOMAC function scores had improved in both groups but were lower in the HA group (MD 5.80;

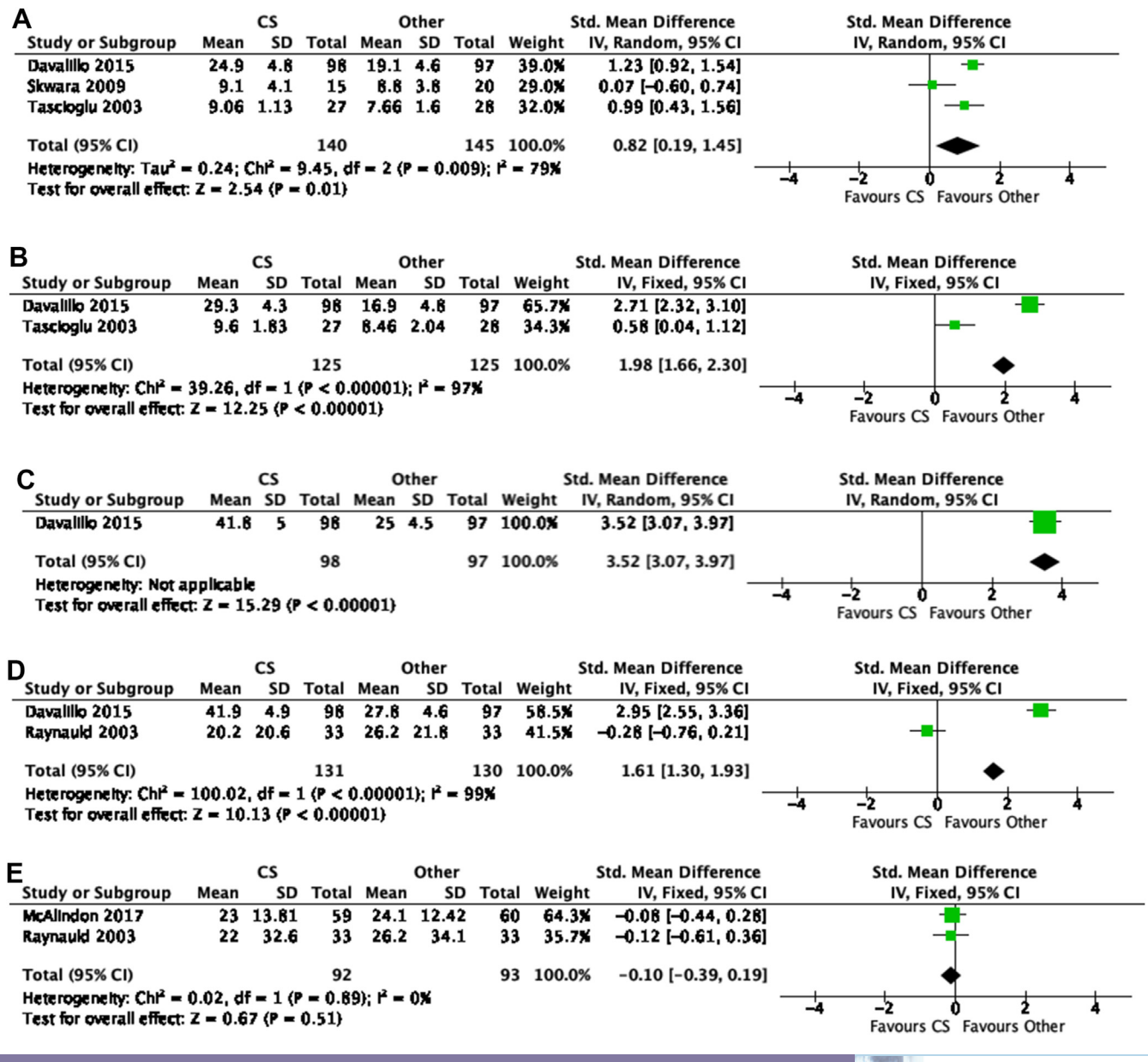

Fig. 3

Osteoarthritis and Cartilage

Forest plots demonstrating differences in WOMAC function scores for CS vs 'other' in patients with knee OA at 3 months (3A), 6 months (3B), 9 months (3C), 12 months (3D) and 24 months (3E).

95% CI 4.48, 7.12; $p < 0.00001$). This trend was also seen at 6 months (MD 12.40; 95% CI 11.12, 13.68; $p < 0.00001$), 9 months (MD 16.80; 95% CI 15.47, 18.13; $p < 0.00001$), and 12 months (MD 14.10; 95% CI 12.77, 15.43; $p < 0.00001$).

CS vs saline in patients with knee OA[28,31]

Pain

Both studies assessed VAS pain scores (scale 0–100). Although improvements were seen in both the CS and saline groups, no differences were noted between treatment groups at 12 months (MD −0.40; 95% CI 9.65, 8.85; $p = 0.93$), and 24 months (MD −0.52; 95% CI −8.85, 7.81; $p = 0.90$).

Function

Both studies assessed function using the WOMAC function scale (scale 0–68). Overall function improved in both the CS and saline groups; however, there were no differences between the groups at 12 months (MD −6.00; 95% CI −16.23, 4.23; $p = 0.25$) and 24 months (SMD −0.10; 95% CI −0.39, 0.19; $p = 0.51$).

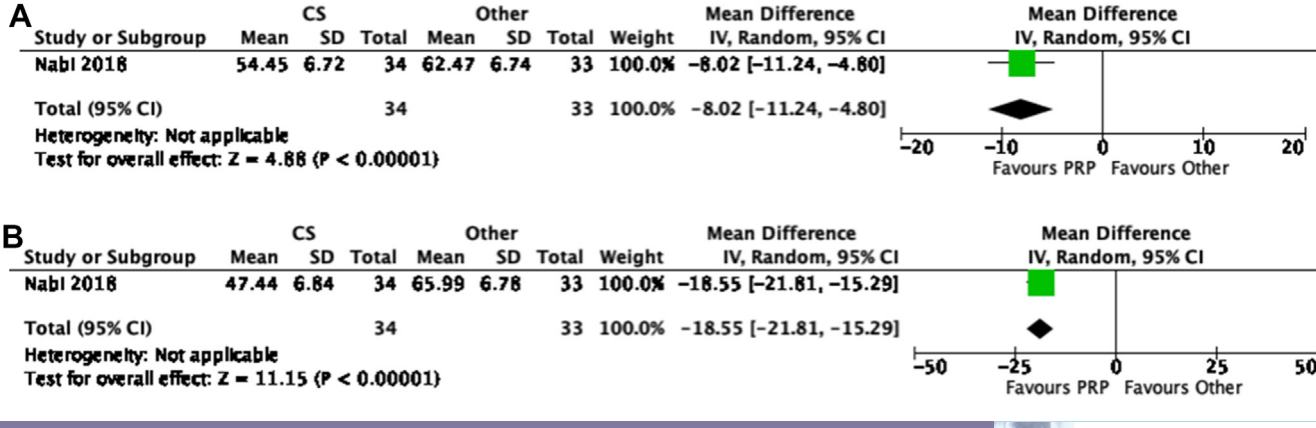

Fig. 4

Osteoarthritis and Cartilage

Forest plots demonstrating differences in KOOS ADLs scores for CS vs 'other' in patients with knee OA at 3 months (4A) and 6 months (4B).

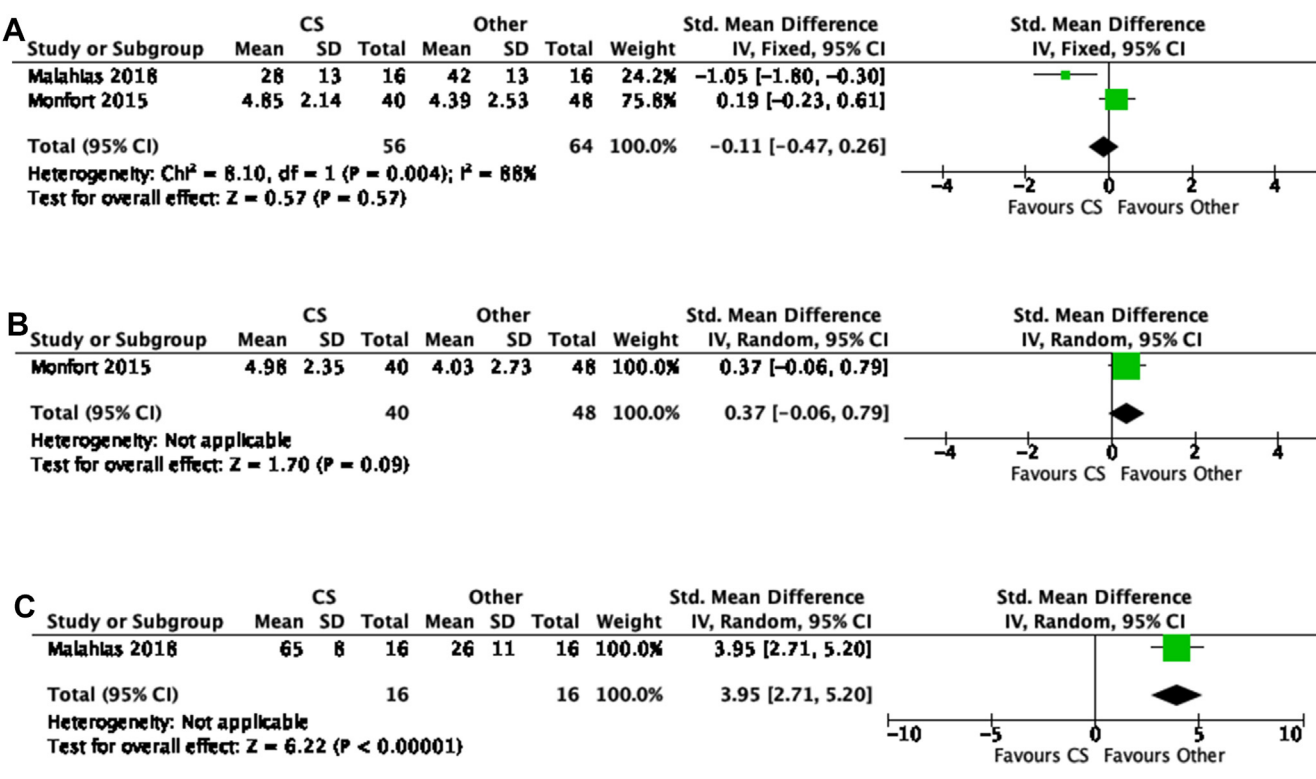

Fig. 5

Osteoarthritis and Cartilage

Forest plots demonstrating differences in VAS pain scores for CS vs 'other' in patients with knee OA at 3 months (5A), 6 months (5B) and 12 months (5C).

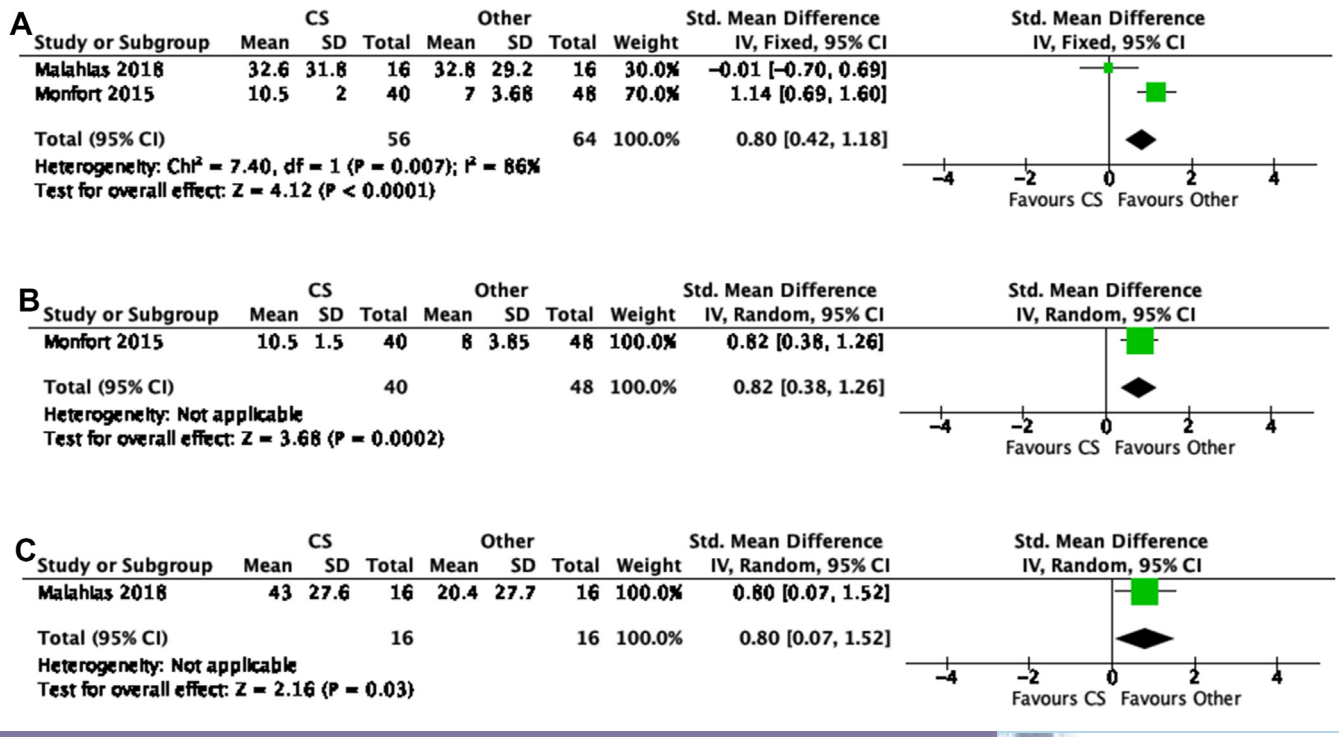

Fig. 6

Osteoarthritis and Cartilage

Forest plots demonstrating differences in VAS pain scores for CS vs 'other' in patients with knee OA at 3 months (6A), 6 months (6B) and 12 months (6C).

Radiographic outcomes

McAlindon *et al.* evaluated several radiographical parameters. At 24 months, the total mean cartilage thickness (mm) was lower in the CS group (MD −0.19; 95% CI −0.37, −0.01; $p = 0.04$), as was the total cartilage damage index (mm^3) (MD −119.28; 95% CI −228.08, −10.48; $p = 0.03$). However, at 24 months, there was no difference in the total area of denudation (mm^2) (MD −0.05; 95% CI −1.27, 1.17; $p = 0.94$), the bone marrow lesion volume ($log(mm^3)$) (MD 0.77; 95% CI −1.23, 2.77; $p = 0.45$) nor the effusion volume ($log(mm^3)$) (MD 0.13; 95% CI −0.32, 0.58; $p = 0.57$).

Discussion

Key findings

To our knowledge, this is the first comprehensive meta-analysis of the longer-term outcomes (at 3 months and beyond) of the effects of recurrent IACIs compared to other intra-articular treatments, placebo, or no treatment. Only ten RCTs were identified in the literature: eight for knee OA and two for trapeziometacarpal OA. Whilst the risk of bias for the individual studies was assessed as low, there was significant heterogeneity between studies which created challenges for the meta-analysis. Our analysis was segregated by the index joint, and then by different groups of interventions and comparators to reduce heterogeneity in the results.

Whilst the RCTs demonstrated improvements from baseline in pain, function, QoL, stiffness and radiographical attributes for recurrent IACIs beyond 3 months and up to 24 months, in many cases, the comparators (including placebo) demonstrated an equal or superior effect, or the effect attenuated at the maximal duration of follow-up. In many cases, alternative injectables (particularly HA and PRP) provided greater symptomatic benefits over the longer-term. Recurrent IACIs failed to demonstrate superiority over placebo (saline) for pain and function after 12- and 24-months post-injection. Most notably, none of the included studies assessed important longer-term outcomes such as the systemic side-effects of recurrent IACIs, whether recurrent IACIs accelerate OA, the time-to-future surgical interventions (e.g., arthroscopy or arthroplasty), or the risk of future prosthetic joint infection (PJI).

Comparison to existing work

The recommendations made by several national and international bodies include the use of intra-articular injections for the non-surgical treatment of OA but the detail of what should be injected for which conditions appear to be inconsistent. The 2019 Osteoarthritis Research Society International (OARSI) guidelines on the non-surgical management of OA suggest that IACIs may provide short-term pain relief; however, intra-articular HA injections may have beneficial effects on pain at, and beyond, 3 months of treatment, and a more favourable long-term safety profile than recurrent IACIs[34]. The 2014 National Institute for Health and Care Excellence guidelines recommend that IACIs should be considered as an adjunct to other core treatments for the relief of moderate-to-severe pain for OA, but do not recommend intra-articular HA injections for the management of OA[35].

They also acknowledged that steroid-induced arthropathy remains controversial and poorly understood. The 2013 American Academy of Orthopaedic Surgeons (AAOS) guidelines do not promote or discourage the use of IACIs (or PRP) in patients with OA, stating that the existing literature remains inconclusive, but did not recommend the use of intra-articular HA injections[36]. The 2018 European League Against Rheumatism (EULAR) recommendations for the management of hand OA advised against the use of IACIs except in patients with painful interphalangeal OA[37].

There is a growing body of evidence to suggest that IACIs may not be as safe as previously thought, leading to complications including accelerated OA progression, subchondral insufficiency fractures, osteonecrosis, and rapid joint destruction, albeit the evidence is not robust[38]. A 2017 observational study suggested that patients who were administered IACIs before undergoing a total knee replacement (TKR) were at an increased risk of postoperative infection and that there was a time-dependent relationship with an increased risk of infection if the time between interventions was lower[39]. A 2015 review also raised concerns regarding IACIs having time- and dose-dependent catabolic effects on cartilage morphology, histology and viability in both *in vivo* and *in vitro* studies[40]. Further longitudinal data is required to assess longer-term harms and benefits to patients undergoing recurrent IACIs.

Implications of our findings

The existing literature is limited by insufficient follow-up and has not sought to adequately measure outcomes such as the time-to-future surgical interventions. The RecUrrent IACIs in Osteoarthritis (RUbICOn) study designed by our group intends to establish the long-term safety and outcomes of the use of recurrent IACIs using linkage of large datasets (Clinical Practice Research Datalink (CPRD) with linkage to Hospital Episode Statistics (HES) and National Patient-Reported Outcomes Measures (PROMs)), as well as establishing the views and experiences of patients and clinicians[41,42]. This may provide further insight on the longer-term effects of recurrent IACIs, and help to inform existing guidelines and future research.

Limitations

There were numerous limitations to this meta-analysis. First, the number of patients in the intervention and comparator groups were generally small, with seven of the ten included RCTs having fewer than 50 patients in each treatment arm. Second, seven of the ten included studies were single-blinded (mostly blinding of the observer but not the patient), thus increasing the risk of bias. Third, as Table I demonstrates, there was heterogeneity concerning the medicines injected, their doses, their frequency, and the duration of follow-up, hence the results should be interpreted with caution. Fourth, no study attempted to detail the minimal clinically important difference (MCID) for outcome measures, i.e., the smallest difference in the score that patients perceive as beneficial, since the MCID and statistical significance do not always correlate. Finally, it should also be noted that one study[26] dates back to 1984 and the quality of research processes has drastically improved since then. Three studies[28,30,31] received local/national funding; the remaining studies declared no conflicts of interest.

Conclusion

This study demonstrates that recurrent IACIs often provide inferior (or non-superior) symptom relief compared with other injectables (including placebo). Whilst mild improvements in pain, function and QoL were noted after recurrent IACIs up to 3–24 months post-injection compared to baseline symptoms, other injectables (HA and PRP) often yielded greater improvements. Recurrent IACIs did not outperform placebo (saline) for pain and function at 12- and 24-months. Existing RCTs on recurrent IACIs lack sufficient follow-up data to assess disease progression and time-to-future intervention. Future research should seek to identify whether recurrent IACIs pose significant long-term harms.

Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol for the submitted work. AJ, AWB and MRW disclose financial activities, outside the remit of the submitted work (AJ: personal fees; AWB: research grants; MRW: research grants, lecturing, textbook royalties); no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2022.07.011.

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