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Stem cell injections in knee osteoarthritis: a systematic review

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ABSTRACT

Objective Stem cell injection for knee osteoarthritis (KOA) is an emerging new therapy, and we aimed to review its evidence of efficacy.

Design Systematic review.

Eligibility criteria Criteria for eligibility were randomised controlled trials (RCTs) and non-RCT on the efficacy of stem cell injections in KOA. All references were checked for missed articles.

Data sources MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, PEDro and SPORTDiscus were searched. A grey literature search was performed. No restrictions were imposed to our search strategy.

Risk of bias and data synthesis Risk of bias was assessed using the Cochrane risk of bias tool. Descriptive synthesis was performed using the levels of evidence according to the Oxford Levels of Evidence.

Results Five RCTs and one non-RCT were found. Bone-marrow-derived stem cells, adipose-derived mesenchymal stem cells and peripheral blood stem cells were used. All trials were at high risk of bias, resulting in level-3 evidence. All five RCTs reported superior efficacy for patient-reported outcomes (Visual Analogue Scale, Western Ontario and McMaster Universities Arthritis Index, Tegner, Lysolm, International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score, Lequesne) compared with controls at final follow-up (range 24–48 months). Superior radiological outcomes were found favouring stem cell injection. Superior histological outcomes and/or improved arthroscopically scored healing rates were reported in two trials. No serious adverse events were reported.

Conclusion Six trials with high risk of bias showed level-3 or level-4 evidence in favour of stem cell injections in KOA. In the absence of high-level evidence, we do not recommend stem cell therapy for KOA.

INTRODUCTION

Knee osteoarthritis (KOA) is a common chronic condition affecting between 6% and 40% of the general population[1 2] and is significantly increased among retired elite athletes, with prevalence rates as high as 95%.[3–5] The global burden of disease of KOA as rated by the WHO in its 2011 reports is comparable with that of patients with cardiac dysrhythmias, liver cirrhosis or stage IV kidney disease.[6] The primary treatment of KOA includes exercises, weight reduction and analgesics or non-steroidal anti-inflammatory drugs.[7–10] In cases where these interventions are insufficient, many non-invasive therapies such as corticosteroid injections,[11] hyaluronic acid (HA) injections,[12] platelet-rich plasma (PRP)[13] and glucosamine[14] have been evaluated with varying results.[7 9–16] Surgical interventions such as osteotomy or total knee arthroplasty remain a last resort.[7 8 17–19]

In recent decades, stem cells have emerged as a possible treatment modality for KOA in humans.[20 21] These pluripotent or multipotent cells have the capability of differentiating into several cell lineages.[22] Mesenchymal stem cells (MSCs) are popular due to their ease of harvesting,[23] safety[24 25] and potential to differentiate into chondral tissue.[24] Whether this aspect of stem cells is sufficient to be of additional value in the treatment of KOA remains open to discussion, as research has shown that after injection, few cells survive or remain in situ.[26–28] Other than their potential for differentiation, stem cells possess paracrine and immune-modulating effects through growth factor and cytokine release.[29–32] Considering that the pathophysiology of KOA is considered both degenerative and inflammatory,[24 31] stimulation of local growth, reducing the immune response and tissue regeneration may be of beneficial effect on this condition.

Several recent reviews,[20 24 33–35] including one systematic review with meta-analysis,[33] reported beneficial effects of stem cell therapy in KOA, although insufficient evidence remains available to recommend its use.[20 24 33–35] However, these reviews were not systematic by nature,[20 24 35] included animal models or performed suboptimal quality assessment.[34] This may have resulted in missed articles or overly positive conclusions. In 2015, Xia *et al*[33] performed meta-analysis of seven studies and found poor evidence to support the use of stem cells in the treatment of KOA. Both clinical and statistical heterogeneity was present in the analysed data, which was not investigated. We equally felt that the methods for including possibly unpublished trials were limited in this review.

As the amount of published trials within the field of stem cell research is fast growing, and more clinics are offering stem cell treatments,[36] we believe patients will soon present themselves to regular care practices with questions about stem cell treatment. Furthermore, we considered the aforementioned reviews lacking in rigorousness to tackle heterogeneity, risk of bias assessment and publication bias assessment. These combined reasons led us to perform this systematic review, which aims to critically evaluate the currently available evidence of the efficacy of stem cell injections in KOA.

MATERIALS AND METHODS

This review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic

Box 1 Inclusion criteria

- Trial with participants with any degree of primary or secondary osteoarthritis of the knee diagnosed by an experienced clinical physician
- Trial evaluated the injection of stem cells of any origin into the affected knee compared with any other intervention, placebo and/or a control group. All dosages, timing variations and delivery systems are included
- Trials including injection of stem cells combined with another intervention are included if this combined intervention is compared with an intervention without stem cell injection or a placebo injection
- Trials describing a minimal proof of stem cell injection (ie, analysis of cell count or typing)
- Trials that assessed the effect of intra-articular injection of stem cells on patient-reported outcome measures, pain, a validated imaging scoring system and/or adverse effects

Reviews and Meta-Analyses) statement.[37] A full version of the protocol was registered on PROSPERO (crd42015022084). We systematically searched the literature for trials evaluating the effect of intra-articular stem cell therapy without restrictions of time, language or content. The full inclusion criteria are available in box 1. Randomised controlled trials (RCTs) and non-RCT (nRCT) were included. No restrictions in language or time were imposed. Both published and unpublished trials were eligible for inclusion if data were available. All possible patient-reported outcome measures (PROMs), pain, radiologic outcomes and adverse events were included for review.

Search methods

We searched the following literature sources for relevant reports of individual studies: PubMed, EMBASE, CINAHL, Web of Science, Cochrane Library, PEDro and SPORTDiscus. Databases were searched without language or time restrictions until 1 May 2016 using a search strategy designed by a research librarian. The exact search terms can be found in see online supplementary appendix 1. All citations were downloaded into an electronic citation manager (Zotero, Roy Rosenzweig Center for History and New Media, Fairfax, Virginia) by one author (MK), and duplicates were removed. References of included trials were searched for trials that may have been missed during this search.

Next, one author (MW) searched unpublished and ongoing studies by using free-text terms (stem cell and knee). These sources were searched from their inception to June 2016.

The following grey literature databases were searched: Open Grey (http://www.opengrey.eu/), British Library Inside (http://searcharchives.bl.uk/) and BIOSIS Previews (www.ovid.com).

For ongoing studies, the following trial registers and registries were searched: WHO International Clinical Trials Registry Platform (http://apps.who.int), US National Institutes of Health Trial Register (www.clinicaltrials.gov), European Clinical Trial Register (www.clinicaltrialsregister.eu) and the ISRCTN (International Standard Randomised Controlled Trial Number) registry (http://www.isrctn.com).

STUDY SELECTION

Two authors (MK and MM) reviewed all titles and abstracts from the first search. Full texts of possible eligible trials were obtained and translated, if necessary, by a professional medical translator. Then, both authors read full-text content and independently assessed eligibility by applying our inclusion criteria (see box 1). In case of disagreement between authors, a consensus meeting was organised. If no consensus could be reached, a third author (HP) was consulted.

For the grey literature (unpublished and pending trials), two authors (HP and MW) reviewed all titles and abstracts that were identified during the search. The listed contact persons of possible eligible trials for review were contacted by one author using a standard e-mail. In case the contact person did not respond within 3 weeks after the e-mail was sent, the trials' data were considered unavailable. If data were made available through a full-text manuscript for analysis, they were screened for eligibility using the inclusion criteria (box 1), and if eligible, they were included in the analyses.

Data extraction

A standardised data extraction sheet was used to extract the following data: study design, population, inclusion and exclusion criteria, outcomes, effect measures, stem cell type, culturing mode, implantation mode, concomitant surgery, adverse events and placebo or control intervention. Data were extracted by one author (HP) and checked by a second author (MW). Differences in the interpretation of data were resolved during a consensus meeting. If no consensus could be reached, a third author (MM) was consulted.

RISK OF BIAS ASSESSMENT OF INDIVIDUAL STUDIES

Two reviewers (MW and HP) independently assessed the quality of the included studies using the Cochrane risk of bias tool,[38] with a priori formulated criteria adopted from the work of Winters *et al*[39] (see online supplementary appendix 2). Five domains of bias were appraised: selection bias (random allocation and allocation concealment), performance bias (blinding of personnel and participants), detection bias (blinding of outcome assessment), attrition bias (loss to follow-up), reporting bias (outcome reporting) and other biases. Each item was scored as to be at low (+), high (–) or unclear (?) risk of bias. The ratings of the risk of bias were equally adapted and slightly modified from the work of Winters *et al*.[39] Studies were considered at low risk of bias when all domains were scored as low risk of bias or if one item was scored as high risk or unable to determine. If two domains were scored as high or unable to determine risk of bias, the study was considered at moderate risk of bias. Finally, when more than two domains were scored as high risk of bias, the study was regarded as being at high risk of bias.

In case of disagreement between assessors, consensus was sought during a consensus meeting. If no consensus was reached, a third assessor (MM) was asked to give a final verdict.

DATA SYNTHESIS

We planned a meta-analysis for RCTs when studies were clinically homogeneous (ie, identical stem cell type, cointervention, control intervention and outcome assessment) and at low or moderate risk of bias. If meta-analysis was not possible, a descriptive synthesis was carried out, in which the impact of individual studies was considered in light of its risk of bias and sample size. The Oxford Levels of Evidence[40] were used to evaluate the level of evidence for each trial (see table 1). A trial was downgraded in case of high risk of bias.

RESULTS

Study selection

Figure 1 illustrates the study selection. After removal of duplicates, a total of 687 articles were screened. Five eligible

Table 1 Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence for interventions[40]

Level 1	Systematic reviews
Level 2	Randomised controlled trials with low/moderate risk of bias or observational studies with dramatic effect
Level 3	Non-randomised controlled trials with low/moderate risk of bias or randomised controlled trials at high risk of bias
Level 4	Case series, case-control studies, historically controlled studies or non-randomised controlled trials at high risk of bias
Level 5	Mechanism-based reasoning/expert opinion

trials[41–45] were identified, and reference checking revealed one additional trial.[46] One of these trials[46] was written in Chinese, and a professional translation was obtained. Trial register search (figure 1) yielded 32 possible eligible trials (see online supplementary appendix 3), but no additional full text reports could be obtained. The grey literature database search yielded no additional relevant reports.

Study characteristics

Table 2 summarises the article characteristics. Five RCTs[42–46] and one nRCT[41] were included. The number of patients injected with stem cells ranged between 15 and 36. A total of 155 patients were treated with a variety of stem cells, and a total of 155 patients served as controls.

One trial[43] performed eight postoperative injections 1 week after surgery, with a 1-week interval for the first five injections. The final three injections were given after 6 months, with weekly intervals. Five trials[41 42 44–46] performed only one injection either peroperatively,[42] postoperatively[41 45 46] or as a single intervention.[44]

Four trials[42–45] performed immunophenotypic characterisation of the MSCs. Two trials[41 46] used a cell counter to count the number of injected cells. One of these trials[41] reports the use of a viable cell analysis using the methylene blue dye exclusion test.

HA and PRP were used concomitantly with the injected MSCs in five trials[41–45] and used as monotherapy for the control groups. One trial[46] did not use any concomitant injectable treatment, and the control group received no placebo injection.

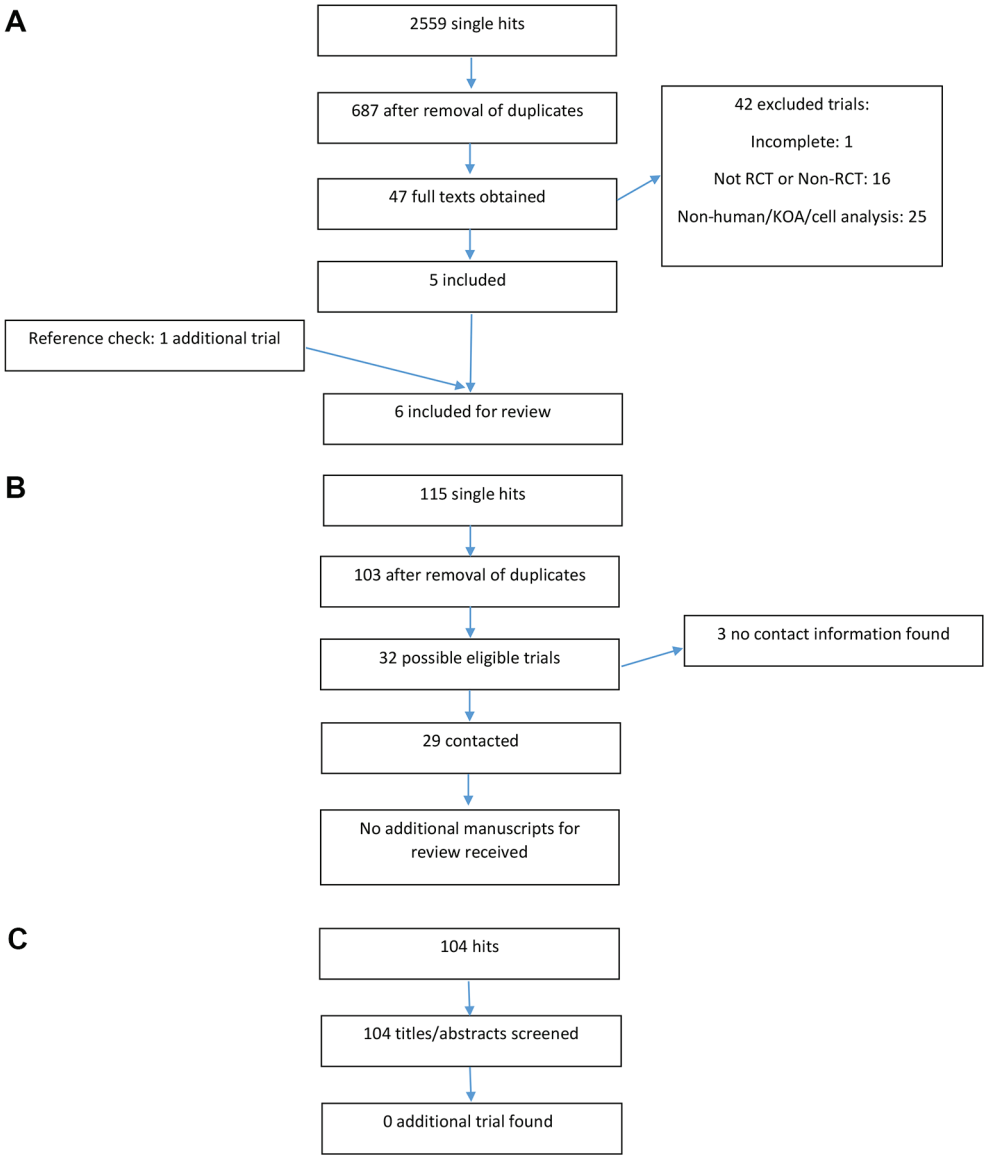

Figure 1 (A) Regular database search flow diagram. (B) Trial registers search flow diagram. (C) Grey literature database search flow diagram. KOA, knee osteoarthritis; RCT, randomised controlled trial.

Table 2 Study characteristics

Author(s)	Year	Study type	n	Mean age*	% women	Last follow-up	Stem cell type	Culturing	Surgical procedure	Number of intra-articular injections	Timing of injection	Concomittant and control injection	Level of evidence
Koh *et al*[41]	2012	Non-RCT	25 Int., 25 control	Cases: 54.2/–9.3, control 54.4/–11.3	Int.: 68% Control: 68%	16.4 mo (range 12–18 mo)16.4 mo (range 12–18 mo)	Autologous adipose-derived MSC	no	Arthroscopic debridement	1	Same day as arthroscopy	PRP	4
Saw *et al*[43]	2013	RCT	25 Int., 25 control (1 LTFU)	Int: 38 /–7.3 control: 42/–5.9	Int.: 60% Control: 71%	24 mo	Autologous peripheral blood stem cells	No	Arthroscopic subchondral drilling	8	1 week postoperative, first five every week, last three after 6 mo, with weekly intervals	Hyaluronic acid	3
Wong *et al*[45]	2013	RCT	28 Int., 28 control	Int. 53 (med) range 36–54 control 49 (med) range 24–54	Int.: 54% Control: 50%	Int. 24.8 mo (range 24–36 mo) Control 24.5 mo, (range 24–35 mo)	Autologous bone-marrow-derived stem cells	Yes	Arthroscopic microfracture and open- wedge high tibial osteotomy	1	Median 22 postoperatively	Hyaluronic acid	3
Tan *et al*[46]	2013	RCT	36 Int., 36 control	Int 53.4 /–6.9 control 53.7 /–5.7	Int.: 72% Control: 75%	12 mo	Autologous bone-marrow-derived stem cells	Yes	Arthroscopic debridement	1	1 mo after arthroscopy	None	3
Koh *et al*[42]	2014	RCT	26 Int. (3 LTFU, 2 no second arthroscopy), 26 control (2 LTFU, 1 no second arthroscopy)	Int. 54.2 /–2.9 control 52.3 /–4.9	Int.: 76% Control: 74%	24.4 mo (range 24–25 mo)	Autologous adipose-derived MSC	No	Open-wedge high tibial osteotomy	1	Peroperatively	PRP	3
Vega *et al*[44]	2015	RCT	15 Int., 15 control	**Int. 56.6 /–9.6 Control 57.3 /–9.4	Int.: 60% Control: 67%	12 mo	Allogenic bone-marrow-derived stem cells	Yes	None	1	na	Hyaluronic acid	3

*Rounded down to one decimal, where necessary.
**Calculated from trial data.
Int. intervention; LTFU, loss to follow-up; med, median; mo, months; MSC, mesenchymal stem cells; na, not applicable; PRP, platelet-rich plasma; RCT, randomised controlled trial.

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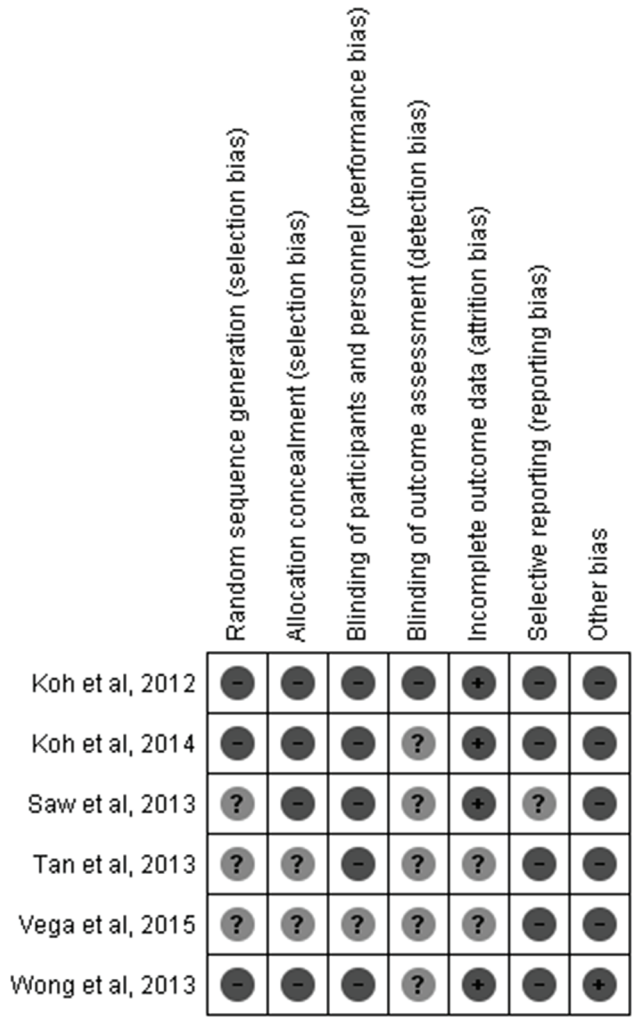

Figure 2 Risk of bias assessment.

Risk of bias assessment

All studies assessed were at high risk of bias (see figure 2 and online supplementary appendix 4).

None of the studies[41–46] performed adequate blinding of patients, care giver and researcher, leading to a high risk of performance bias. A majority[42–46] of the studies did not explicitly describe if and *how* they controlled for detection bias. A high risk of selection bias was deemed to be present for most studies due to the use of quasirandomisation procedures[41 42 45] or a lack of allocation concealment.[41–43 45] Outcome switching and selective outcome reporting could not be excluded. For most trials,[41–43 45 46] no protocol was found in trial registers. Many interim follow-up assessments were reported in the Methods section of five studies,[41 42 44–46] but no findings for these follow-up measurements were reported. Other risk of bias items included incorporating baseline findings into outcome assessment, per-protocol analysis instead of intention-to-treat analyses and data dredging through performing unforeseen analysis or combining outcomes.

Effect of stem cell therapy

Table 3 summarises the outcomes of the intervention groups versus the control groups of all trials.

Due to a high risk of bias across studies and the heterogeneity in terms of (co)interventions, outcome measures used and length of follow-up, no data synthesis was performed. Instead, we present a descriptive synthesis.

Uncultured concentrated autologous adipose-derived stem cells

Two trials[41 42] by the same author treated KOA with uncultured concentrated autologous adipose-derived stem cells in combination with PRP. The concomitant surgical intervention (arthroscopic debridement[41] and open-wedge high tibial osteotomy (HTO)[42]) differed between trials.

The baseline characteristics of both groups differed significantly, with controls showing better baseline scores in the 2012 trial.[41] After a mean follow-up of 16.4 months, Lysholm scores, Visual Analogue Scale (VAS) and Tegner scores did not differ between groups. Radiographic analysis was performed (standard weight-bearing radiographs); however, no data were reported.

In the 2014 trial,[42] after a mean follow-up of 24.4 months, the between-group VAS, Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales pain and symptoms scores were superior for the goup injected with MSCs. Lysholm and the remaining KOOS subscales (activities of daily living (ADL), quality of life, sports and recreation) scores did not differ significantly. Second-look arthroscopically scored Chondral healing was evaluated with the Kanamiya grading system during second-look arthroscopy (performed at a mean of 19.8 month postoperatively) and was superior for the stem cell group compared with controls ($p=0.23$).

Autologous bone-marrow-derived stem cells

Wong *et al*[45] and Tan *et al*[46] used cultured autologous bone-marrow-derived stem cells after either arthroscopic debridement[46] or arthroscopic microfracturing and open-wedge HTO.[45]

Patients in the trial by Wong *et al*[45] received either one injection of HA and stem cells or HA only at a median of 22 days after surgery. Two more HA injections were given at a later time. After a mean follow-up of 24.4 months and after statistical adjustments for age, baseline scores and time of evaluation, significant improvements of International Knee Documentation Committee (IKDC), Tegner and Lysolm scores were in favour of the stem cell group. Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) showed a significant age-adjusted improvement in favour of stem cell therapy.

One month after debridement, patients in the trial by Tan *et al*[46] were injected with bone-marrow-derived stem cells. Controls received no injection. Knee cartilage thickness was assessed using T2-weighted MRI and showed significantly superior improvement in the stem cell group. The Lequesne index decreased significantly at final follow-up, favouring the intervention group.

Allogenic bone-marrow-derived stem cells

Vega *et al*[44] investigated the effect of HA and allogenic bone-marrow-derived stem cells obtained from three healthy donors and compared this with HA only. At 12 months, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, WOMAC general, Lequesne and VAS pain were superior in the stem-cell-treated group compared with the controls based on the standardised mean differences. Short-form health survey 36 did not differ significantly between groups. T2weighted MRI showed no differences between groups at 12 months.

Table 3 Study outcomes

Author	Mean number of cells	Main outcomes	Intervention final FU score	Control final FU score	Mean difference	95% CI	p Value*	adverse events
Koh *et al*[41]	1.89×10^6 (range $1.2–2.3\times10^6$)	Lysolm score Tegner activity scale VAS for knee pain Radiographic evaluation†	68.1/–18.5 2.8/–1.2 2.7/–1.8 NA	69.4/–20.4 2.9/–1.0 2.2/–1.7 NA	NA NA NA NA	–8.4 to 1.2 –0.75 to 0.51 –0.52 to 1.48 NA	p=0.81 p=0.71 p=0.34 no data	1 case of pain and swelling after injection, spontaneously resolved. Unclear if cases of controls. 4 cases of Post injection pain 2–3 days. Unclear if cases or controls.
Saw *et al*[43]	20.6×10^6§	IKDC scores MRI score‡ ICRS II score (n=32)	74.8 9.9 957	71.1 8.5 1066	NA NA NA	NA NA NA	0844 0013 I 0022 I	Pain at injection site (7 int., 7 controls) Delayed pain at injection site (2 int., 3 controls) swelling in knee (15 int., 8 controls) delayed swelling in knee (12 int., 8 controls) difficulty moving knee (10 int., 11 controls) delayed difficulty moving knee (8 int., 7 controls) warmth in knee (16 int., 9 controls) delayed warmth in knee (12 int., 8 controls) other (2 int., 0 control) delayed other (1 int., 0 control) deep vein thrombosis (0 int., 1 control)
Wong *et al*[45]	$1.46/–0.29\times10^7$	IKDC scores Lysolm Tegner MOCART (1-year FU, mean standardised difference)	NA NA NA NA	NA NA NA NA	7.65 7.61 064 19.6	3.04 to 12.26 1.44 to 13.79 0.10 to 1.19 10.5 to 28.6	0001 I 0.0016 I 0021 I <0001 I	no serious adverse events
Tan *et al*[46]	$20.0–30.0\times10^6$	Thickness of knee cartilage Lequesne Index	4.60/–0.15 5.19/–1.12	3.75/–0.26 10.42/–1.08	NA NA	Not reported Not reported	0000 I 0000 I	not reported
Koh *et al*[42]	4.11×10^6	KOOS pain KOOS symptom KOOS sport and recreation KOOS ADL KOOS QOL VAS pain (100 mm scale) Lysolm Weight-bearing line¶ femero-tibial angle¶ Chondral lesion on second-look arthroscopy	81.2/–6.9 82.2/–7.2 NA NA NA 10.2/–5.7 84.7/–16.2 61.1/–3.4 8.7/–2.3 NA	74.0/–5.7 75.4/–8.5 NA NA NA 16.2/–4.6 80.6/–13.5 60.3/–3.0 9.8/–2.4 NA	NA NA NA NA NA NA NA NA NA NA	Not reported Not reported Not reported Not reported Not reported 0.23 to 0.98 –8.4 to 1.2 –3.50 to 4.51 –1.32 to 1.90 Not reported	<0.001 I 0006 I NS NS NS <0001 I 0375 I 0758 I 0678 I 0023 I	not reported
Vega *et al*[44]	40×10^6	VAS (100 mm scale) WOMAC pain WOMAC general Lequense SF 12 physical SF12 mental MRI quantitative T2 mapping	33 (SE 6) 30 (SE 4) 28 (SE 5) 30 (SE 3) 45 /-11 51 /-12 NA	51 (SE 8) 44 (SE 6) 41 (SE 6) 42 (SE 5) 40 /-8 47 /-11 NA	NA NA NA NA NA NA NA	Na Na Na Na Not reported Not reported Not reported	SMD 0.77 vs 0.48 SMD 1.03 vs 0.39 SMD 1.12 vs 0.34 SMD 0.58 vs 0.19 NS NS NS	no major adverse events.postimplantation pain or effusion with swelling (int/control): 8/9 Unexpected osteoarticular pain and/or inflammation (knee, shoulder, hip, ankle, lumbar) (Int/control) 7/5 Other (Int/control) 8/11

*I indicates the intervention group showed significant improvement compared with controls, while C indicates the control group showed significant improvements compared to the intervention group.
†Plain weight-bearing radiographs.
‡Scoring system according to the work of Mithoefer et al.[65]
§Data received from author.
¶Used to evaluate the effect of the high tibial osteomy that was performed
AOL, activities of daily living; FU, follow-up; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LTFU, loss to follow-up; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; na, not available; ns, not significant; QOL, quality of life; SDM, standardised mean difference; SF12, short form 12; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Autologous peripheral blood stem cells

One week after subchondral drilling, five postoperative autologous peripheral blood stem cells injections combined with HA (controls received HA only) were given, with weekly intervals for the first five weeks, and three additional injections were given after 6 months, with a weekly interval in the trials by Saw *et al*.[43] No significant differences were found between groups for IKDC scores at 24 months of follow-up. MRI scores at 18 months of follow-up and histological analysis (ICRS (International Cartilage Repair Society) II) upon second-look arthroscopy (of 32 patients) after 18 months of follow-up were significantly different in favour of the group treated with stem cells.

Adverse events

Adverse events were reported in four trials[41 43–45] (see table 3). None reported any major events in the intervention groups within a maximum of 2 years of follow-up. One deep venous thrombosis was reported in a control patient.[43] Patients most commonly reported pain, swelling and difficulty with movement.[41 43–45] One trial[44] reported unexpected articular pain in joints other than the knee.

Summary

Five RCTs[42–46] and one nRCT[41] were identified. All were considered at high risk of bias due to inadequate blinding, possible selection and detection biases. All trials were downgraded from level 2 in case of RCTs[42–46] to level 3 and level 4 in case of nRCT.[41] Clinical homogeneity prevented meta-analysis. Descriptive synthesis of the trials shows that all but one[41] found positive results for pain, patient-reported outcomes, MRI outcomes and histological and arthroscopic outcomes, favouring stem cell treatment of different origins (adipose, bone marrow and peripheral blood). Four trials[41 43–45] reported adverse events, with a maximal follow-up of 2 years. None of these adverse events were of serious nature.

DISCUSSION

Our systematic review on five RCTs and one nRCT showed a high risk of bias and individual studies of a level-3 or level-4 evidence for the efficacy of different types of MSC injections in combination with different surgical and non-surgical cointervention for the treatment of KOA when evaluating PROMs, radiological, histological and arthroscopic outcomes. No serious adverse events were reported within a maximum of 24 months of follow-up. Contradictory trial results, heterogeneity in outcome measures, heterogeneity in cointerventions such as surgery, HA or PRP injections, stem cell origin, culturing modes and injection frequency and timing make a general statement for the efficacy of MSC undesirable. We recommend that all trials be reviewed as separate pieces of evidence rather than as a whole.

Stem cells have been investigated in several fields of medicine with varying results.[47–51] Their use in KOA has been previously reviewed by several authors,[20 24 33–35] who concluded that a positive trend can be seen favouring stem cell use, although these results warrant further rigorous and methodologically sound investigation.

One of these reviews[33] performed meta-analysis of the data to provide evidence of efficacy. We refrained from doing this due to the large amount of clinical heterogeneity (as illustrated above), making meta-analysis unreliable, and instead chose to review the individual trials descriptively. By doing this, we were more adequately able to assess the current level of evidence for the use of stem cells in KOA. By refraining from pooling data in any way, we felt we were more objectively giving clinicians the necessary information about the efficacy and risks of such forms of treatment. Equally, we felt that our choice to perform a risk of bias assessment using the Cochrane risk of bias tool allowed us to more accurately assess bias domains such as selection bias (other bias in the case of this review) and attrition bias. The use of a more extensive tool allowed for a more critical appraisal of the available evidence.

Furthermore, an extensive grey literature search was performed to assess the possible presence of publication bias. We identified a substantial amount of pending and completed trials (see online supplementary appendix 3). We were unable to assess the possible presence of publication bias by means of a funnel plot or Egger's test, as only data from six trials were available.[38]

Methodological shortcomings are known to influence results in important ways,[38] and the high risk of bias found in the reviewed trials must be taken into account when interpreting the studies' findings. None but one[44] of the studies blinded the participants, who unfortunately failed to describe *how* they were blinded. This was considered an unclear risk of bias. With regard to detection bias, only one study[44] reported that the outcome assessor was blinded to group allocation. For all trials,[41–46] no information was provided on *how* they blinded the outcome assessor. Lack of blinding of participants allowed for a high risk of performance bias to be present in the studies. This is suggested to influence results[38] and may have led to overly positive outcome reporting by both participants and assessors. A high risk of selection bias was present in most studies. Two studies[42 45] asked patients to choose between identical envelopes. As it was not described if these envelopes were opaque, concealment may have been breached, which may also have compromised the random allocation sequence. Other studies[44 46] stated that their procedure was 'random' without describing their methods. As with inadequate blinding, the lack of adequate randomisation methods and allocation concealment have been shown to lead to overly positive results,[38] which may explain some of the between-group differences. Selective outcome reporting is another threat to internal validity. Most of the studies planned interim assessments, but these follow-up outcomes were not reported.[41 42 44–46] Only one trial[44] registered a protocol and, thus, could be checked fully for selective reporting. It is possible that selective reporting may have led to an overly positive presentation of the efficacy of stem cell injection in KOA.[38]

It should be noted that all but one trial used a surgical cointervention. These varied in known efficacy.[7 8] The use of surgical cointerventions introduces performance bias, as the personnel performing the surgical interventions could not be blinded. Therefore, all studies were downgraded for their overall high risk of bias, delivering level-3 or level-4 evidence for the different types of MSCs in combination with surgical and non-surgical cointerventions in the treatment of KOA.

The characteristics of MSCs, which are proposed to have been applied in the investigated trials, include self-renewal capability and the ability to differentiate into osteocytes, chondrocytes, adipocytes, hepatocytes, myocytes, neurons and cardiomyocytes.[32 52–55] Furthermore, in congruence with the criteria formulated by the International Society for Cellular Therapy, these cells are characterised by their plastic adherence and phenotypic characterisation with positive CD44, CD73, CD90 and CD105 surface antigens and negative hematopoietic markers CD3, CD14, CD19, CD34 and CD45.[56] It should be noted that though all trials proposed to have used MSCs, within the identified trials, phenotypic characterisation as described here was only performed in four trials.[42 44 45] Saw *et al* could

only provide us with CD34 cell counts, which is more suggestive of hematopoietic stem cells.[56 57] The other two trials[41 46] did not perform any specific immune-phenotypic characterisation, making their claim of having used MSCs questionable.

Concerns about their safety remain among clinicians.[21] Two systematic reviews of clinical trials (including case series) evaluating MSCs administered both locally and systemically with follow-up of up to 75 months found no serious adverse events.[25 58] One of these systematic reviews[58] performed meta-analysis of randomised and non-randomised clinical trials evaluating systemically introduced MSC. It reported no significant difference between treated and untreated patients for long-term adverse events such as death or malignancy. It should, however, be noted that the follow-up time in this analysis was limited up to a maximum of 60 months, and the confidence intervals of the OR for the malignancy analysis had a wide range, from 0.77 to 9.11, still allowing for a chance of considerable risk. Indeed, in congruence with these findings, the four trials[41 43–45] in this review that reported adverse events found no serious adverse events, although follow-up was relatively short (<24 months). The cited evidence suggest that MSCs are relatively safe based on short-term adverse events, and currently, evidence of malignant transformation of MSCs is lacking.[21 25 58] Nonetheless, long-term adverse events are still poorly researched.

Our review has a few limitations. First, the searches, although systematic, were performed by three authors (HP, MW and MK). We do not think that this will have been of influence on our results, considering that a predefined search strategy was used, and all authors were experienced in the use of electronic databases. Second, the timing between the regular database searches and grey literature search also differed. We felt that repetition of the database search within 2 months would yield no important differences, so we refrained from an update at the time. Third, we deviated from the original protocol, as we felt that it was more appropriate to use the Cochrane risk of bias tool[38] instead of the Downs and Black list,[59] as this last list exhibited items focusing on reporting rather than risk of bias and contained many overlapping questions and criteria, allowing broad interpretation differences. Furthermore, the Cochrane risk of bias tool is considered the preferred tool in the *Cochrane Handbook*.[38] We are confident that the use of this instrument allowed for a more valid and robust estimation of risk of bias in the individual studies, and we would like to note that the decision followed only after we had completed our risk of bias assessment with the Downs and Blacks list. The grey literature search was also adjusted, as we found that most trial registers proposed were covered by the international trial registers and registries searched for this review. We have refrained from the use of data synthesis using the Van Tulder method.[60] Although our primary protocol stated its use, we felt that this or similar approaches would not add to the results of this review, as all individual trials were too heterogeneous for combining. Furthermore, this method allows for accumulation of poor-quality trials and underpowered trials, unjustly leading to a stronger level of evidence. During the course of the review, we planned to use the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[61] Unfortunately, it could not be used, as we did not perform a data synthesis, and publication bias could not be assessed. Finally, one additional inclusion criterion that required trials to perform some sort of cell analysis was added, because we felt that without cell analysis, trials may have boasted the presence of stem cells without this being true per se. This resulted in one exclusion.[62] On evaluation, this trial was found to be of extremely poor quality and would not have influenced the results of our review. Nonetheless, we are convinced this review provides clinicians with an up-to-date overview of the possible efficacy of stem cell injections in KOA.

Recommendations for research

There is no high level of evidence for stem cell therapy in the treatment of patients with KOA due to the high risk of bias in all studies in this review. In congruence with the recently updated International Society for Stem Cell research guidelines,[63] we recommend the following improvements for future studies.

There is a need for rigorous standardised methodology in studies investigating stem cell therapy in KOA. First, reports should keep with the CONSORT (Consolidated Standards of Reporting Trials) statement.[64] Studies should aim to generate random allocation sequences and blind the researcher responsible for randomisation to the patient at randomisation. Blinding of participants, medical personnel, outcome assessor and statistician is essential for securing unbiased estimates of effect. Protocols should be published in trial registers before the study's start to enable the assessment of reporting bias and outcome switching for individual trials and to enable the detection of publication bias in general. Characterisation of the stem cells (MSCs) should be done in accordance with international recommendations[56] in order to provide heterogeneous samples and allowing, eventually, for dose–effect analyses to be possible. We recommend, in order to be able to fully evaluate the safety of MSC, that all treated patients should be followed up for an extended period of time.

Recommendations for daily practice

In congruence with the statement by the Australasian College of Sports Physicians,[21] we believe that considering the level 3 or 4 currently available favouring stem cell use in KOA, its use in daily practice is not recommended.

CONCLUSION

There is level-3 or level-4 evidence for the use of stem cell injection of different types in the treatment of KOA when evaluating PROMs, pain and radiographic, arthroscopic and histological outcomes. It should be noted that all treatments were additional to surgery, HA or PRP injections. All studies were found to be at high risk of bias. Therefore, we do not recommend to use stem cell therapy for patients with KOA.

Key messages

What are the new findings?

- The available evidence supporting the use of (mesenchymal) stem cells in knee osteoarthritis is at high risk of bias.
- The long-term risks of stem cell use needs further investigation.
- Methodologically sound research is needed to explore the efficacy of stem cell therapy in knee osteoarthritis.

How might it impact on clinical practice in the near future?

- Presently, clinicians should refrain from using (mesenchymal stem cells) in patients with knee osteoarthritis.
- If patients are treated with (mesenchymal) stem cells, they should be extensively monitored.
- International guidelines for quality control should be used and followed when working with (mesenchymal) stem cells.

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Stem cell injections in knee osteoarthritis: a systematic review of the literature

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Notes