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SUMMARY WITH CRITICAL APPRAISAL

Intra-Articular Hyaluronic Acid for Osteoarthritis of the Hip or Ankle: A Review of Clinical Effectiveness

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Context and Policy Issues

Osteoarthritis is a disorder caused by damage to articular cartilage, most commonly in older adults.[1] Aging, changes in metabolism, genetic and hormonal factors, biomechanical changes, and inflammation are all associated with the onset and progression of osteoarthritis.[2] Osteoarthritis can cause symptoms such as pain, limitation of movement, various degrees of inflammation, effusion, and disability.[1,2] Between 2010 and 2031, the prevalence of osteoarthritis has been projected to increase from 13.8% to 18.6% in Canada and the direct cost to increase from $2.9 billion to $7.6 billion Canadian dollars (2010 values).[3]

Current treatment options include medications and surgery.[1] Drugs, such as local analgesics, nonsteroidal anti-inflammatory drugs, intra-articular injection of glucocorticoids, can be prescribed to aid with symptom control.[1] Surgery, such as total hip replacement, is often considered a last resort option for osteoarthritis, due to the risks of surgical complications (such as nerve injuries and dislocation).[1] In addition, these treatment options do not aim to delay the pathological progression of osteoarthritis.[1]

Hyaluronic acid supplementation is another option for the treatment of osteoarthritis.[1] Hyaluronic acid constitutes synovial fluid in the joints and increases the viscosity.[1] It functions as shock absorbent within joints and protects cartilage and surrounding soft tissues.[1] Intra-articular injection of hyaluronic acid has been approved by the US Food and Drug Administration in 1999.[1]

Some evidence has suggested that intra-articular injection of hyaluronic acid is effective in relieving pain associated with ankle osteoarthritis and is clinically effective in hip osteoarthritis.[4] Recently there are studies published to demonstrate the effectiveness of the intra-articular injection of hyaluronic acid for patients with osteoarthritis of the hip or ankle.[1,5,6] There is a need to update the review on intra-articular injection of hyaluronic acid. This report aims to review the clinical effectiveness of intra-articular injection of hyaluronic acid for osteoarthritis of the hip and ankle.

Research Question

What is the clinical effectiveness of intra-articular hyaluronic acid for patients with osteoarthritis of the hip or ankle joint?

Key Findings

One systematic review (SR) on the effectiveness of hyaluronic acid for pain and discomfort associated with hip osteoarthritis and one SR for pain associated with ankle osteoarthritis were included. With respect to osteoarthritis in the hip, no significant differences in pain or adverse events were found when compared with placebo or with methylprednisolone and no differences in function or patients' global assessment were found when compared with methylprednisolone. For osteoarthritis of the ankle, the injection of hyaluronic acid was significantly associated with an improvement in measures of pain and disability scores when compared with saline. The results of this review should be interpreted with consideration limitations that include that the dosages of hyaluronic acid were not described in detail and that many of the studies included in the SRs were case series. Further evidence on the clinical effectiveness of hyaluronic acid in Canada may help to reduce the uncertainties in health policy making.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline via OVID the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were hyaluronic acid and joints or joint disorders. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and May 28, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients, in any setting, with osteoarthritis of the hip or ankle joint
Intervention	Intra-articular injection of hyaluronic acid (any products) for viscosupplementation
Comparator	Placebo; Intra-articular corticosteroid therapy
Outcomes	Clinical effectiveness (e.g., disease severity; changes in pain, joint mobility, functioning, functioning without aids, frequency of treatment injection, requirement for analgesics); and safety (e.g., side effects, adverse events, injection site reaction)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, (non-randomized studies)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded. Systematic reviews with full overlap of eligible included studies were excluded; the most recent comprehensive reviews were selected for inclusion.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 478 citations were identified in the literature search. Following screening of titles and abstracts, 451 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 25 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised two systematic reviews. Appendix 1 presents the PRISMA[8] flowchart of the study selection.

Additional references of potential interest, including the SRs that were excluded due to full overlap of included studies, are provided in Appendix 7.

Summary of Study Characteristics

Study Design

Two relevant systematic reviews (SRs) were included.[9] The SR by Letite, Amadera, and Buehler was published in 2018.[10] Randomized controlled trials (RCTs) published up to March 2017 were searched in multiple databases and nine were included.[10] The SR by Vannabouathong et al. was published in 2018.[9] Vannabouathong et al. searched observational and interventional studies in multiple databases.[9] There were no overlap in the primary studies in the two SRs.[10] The primary studies in the SRs were listed in Appendix 5.

Country of Origin

Letite, Amadera, and Buehler were based in Brasil.[10] Vannabouathong et al. were based in Canada.[9]

Patient Population

There were nine RCTs included in the results section and according to the Study characteristics table there were 1,164 patients in total.[10] In the study characteristics table, the mean ages in the primary studies ranged from 53 to 73 years.[10] The sample sizes in the primary studies ranged from 42 to 357.[10] In the Study characteristics table, 942 participants in six RCTs were eligible for the inclusion criteria of this report.[10] Vannabouathong et al. included data from 1,085 patients with ankle osteoarthritis, rheumatoid arthritis, or hemophilic arthropathy from 27 observational or interventional studies.[9] Of all participants included in the SR, data from 165 were eligible for the inclusion criteria of this report.[9]

Interventions and Comparators

The intervention was intra-articular injection of hyaluronic acid and eligible comparators were placebo (four RCTs) and methylprednisolone (three RCTs) in the SR by Leite, Amadera, and Buehler.[10] Intra-articular injection of hyaluronic acid was the intervention and the comparator was corticosteroids (four studies) in the SR by Vannabouathong et al.[9] One, two, or three injections of hyaluronic acid of various molecular weights from six brands were used in the primary studies in the SR by Leite, Amadera, and Buehler.[10] The dosages of the comparators in the SR by Leite, Amadera, and Buehler were not described.[10] The interventions and comparators in the SR by Vannabouathong et al. were not described in detail.[9]

Outcomes

The primary outcome in the SR by Leite, Amadera, and Buehler was pain (based on various measurement scales).[10] The pain measurement tools used in the primary studies included visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index.[10] The secondary outcomes were disability, quality of life, Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) Responder Index (a scale based on the measures of pain, function, and patient's global assessment)[11] that was validated in a previous study,[11] and adverse events.[10] The follow-up lengths in the primary RCTs were up to 12 months.[10] The outcomes of interest in the SR by Vannabouathong et al. included pain, function, stiffness, quality of life, disease-specific indices, adverse events, patient satisfaction, and tolerability.[9] The outcome measures included visual analog scale, Short-Form 36, Ankle Osteoarthritis Scale, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), American Orthopaedic Foot & Ankle Society score, Foot and Ankle Outcome Score, Japanese Society for Surgery of the Foot, Self-Administered Foot Evaluation Questionnaire, Foot and Ankle Disability Index, acetaminophen consumption, and range of motion.[9] Validation of the questionnaires and minimal clinically significant differences were not reported. The follow-up lengths were up to 30 months in the primary studies.[9]

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Additional details regarding the characteristics of outcome measures are provided in Appendix 6.

Summary of Critical Appraisal

The clarity of reporting is fundamental to understand the results and assess the validity of the results. Only Leite, Amadera, and Buehler published the review protocol *a priori*.[10] The population, intervention, comparator, and outcome criteria in the SRs by Leite, Amadera, and Buehler and Vannabouathong et al. were described.[9,10] The selection of study design was explained in both SRs.[9,10] The included studies were described.[9,10] However, lists of the excluded studies were not provided in both SRs.[9,10] The reporting quality of the SR by Leite, Amadera, and Buehler was not optimal and there was a discrepancy in the number of included primary studies and sample sizes reported in the abstract and the results.[10]

Systematic searches help to decrease the likelihood of omitting important evidence and potential selection bias. Comprehensive literature searches were conducted.[9,10] Independent study selection and data extraction were important to maintain the quality of study execution and reduce human error. However, only Vannabouathong et al. selected studies in duplicate.[9] Leite, Amadera, and Buehler extracted data in duplicate.[10]Appropriate assessment and classification of the risk of bias in primary studies could prevent biased studies from skewing the pooled results. The risk of bias of the included studies were assessed with published tools.[9,10] The impact of risk of bias in the included studies was considered in the meta-analyses.[9,10] The risk of bias in the included studies was considered when interpreting the results.[9,10] Heterogeneity of the results was discussed in the SRs.[9,10] Appropriate statistical methods were used in the SRs.[9,10] The statement of conflict of interests helped readers to understand the potential bias from the study funders. Only Vannabouathong et al. reported the funding sources for the included studies and declared competing interests.[9]

Additional details regarding the strengths and limitations of included publications are provided in .

Summary of Findings

Clinical Effectiveness of intra-articular injection of hyaluronic acid

Osteoarthritis of the hip

One of the included SRs included studies regarding the clinical effectiveness of intra-articular injection of hyaluronic acid for people with osteoarthritis in the hip.[10] When compared with placebo, the standardized mean difference in pain at three months after the injection of hyaluronic acid and risk ratios of adverse events were not statistically significant.[10] When compared with methylprednisolone, pain at one month after injection, risk ratios of OMERACT-OARSI Responder Index at one month, and risk ratios of adverse events were not statistically significant.[10] When making their conclusions, Leite, Amadera, and Buehler did not recommend intra-articular injection of hyaluronic acid for the treatment of hip osteoarthritis.[10]

Osteoarthritis of the ankle

One of the included SRs included studies regarding the clinical effectiveness of intra-articular injection of hyaluronic acid for people with osteoarthritis of the ankle. Only the results of three RCTs comparing hyaluronic acid and saline using Ankle Osteoarthritis Scale scores as the outcome were meta-analyzed.[9] Other outcomes were reported in studies that were not eligible for this report. When compared with saline, the results of a meta-analysis of three RCTs showed that intra-articular injection of hyaluronic acid was associated with significant improvement in Ankle Osteoarthritis Scale (based on measures of pain and disability) scores six months.[9] In a sensitivity analysis, the RCT by DeGroot et al. was excluded for adopting a single-injection regimen, while five-injection regimens were adopted in the other two RCTs.[9] Hyaluronic acid remained significantly associated with better Ankle Osteoarthritis Scales scores.[9]

Additional detail regarding findings and conclusions are reported in Appendix 4.

Limitations

There were limitations to both quantity and quality of the evidence. There were a limited number of studies included and the sample sizes of the primary studies were not large (357 maximal).[9,10] The most recent trial was conducted in 2017.[9,10] More than half of the included studies in the review by Vannabouathong et al. were case series or non-interventional studies showing significant changes associated with hyaluronic acid without valid comparators.[9] The limitations in study quality were related to the lack of detail in study characteristics and clarity of reporting. The dosage of hyaluronic acid was not described in detail.[9] Other comparators might be preferred in certain settings, such as platelet-rich plasma often tested in recent trials .[10] Not all patients included in the SRs met the inclusion criteria of this report.[9,10]

Conclusions and Implications for Decision or Policy Making

One SR examining osteoarthritis of the hip[10] and one SR examining osteoarthritis of the ankle with one and two limitations in the critical domains of the appraisal tool respectively were included for the assessment of the clinical effectiveness of intra-articular injection of hyaluronic acid.[9] One SR found that there was no significant difference in pain at three months or adverse events between the injection of hyaluronic acid and placebo for patents with hip osteoarthritis.[10] The were no statistically significant differences in pain at one month post-injection, a composite measures of pain, function, and patient's global assessment at one month, and adverse events between the injection of hyaluronic acid and methylprednisolone.[10] The use of hyaluronic acid for the treatment of hip osteoarthritis was not recommended by the SR authors.[10] However, the evidence was limited by small sample sizes and inconsistent reporting.[10]

The other SR on the use of hyaluronic acid to aid with symptoms associated with osteoarthritis of the ankle meta-analyzed three RCTs eligible for this report.[9] Compared to saline injection, hyaluronic acid was significantly associated with an improvement in a measure of pain and disability.[9] In a sensitivity analysis, hyaluronic acid remained significantly associated with an improvement in a measure of pain and disability.[9] The authors concluded that the results from small trials favored hyaluronic acid for the treatment of ankle osteoarthritis.[9] However, this SR was limited by small sample sizes and lack of details in the interventions and comparators.

The clinical effectiveness of hyaluronic acid for the treatment of ankle osteoarthritis was showed in reviews published in 2007 and 2010.[4,12] In the two reports, hyaluronic acid was found to be effective in pain relief for ankle and hip osteoarthritis.[4,12] However, based on updated searches and meta-analyses, the support for the use of hyaluronic acid for hip osteoarthritis was lacking. The reasons for the difference in identified clinical effectiveness were unclear.

For policymakers, the evidence to support the use of hyaluronic acid for osteoarthritis of the hip may be lacking and there is evidence from small trials to support the use of hyaluronic acid for the treatment of osteoarthritis of the ankle. Further effectiveness research on the use of hyaluronic acid in hip and ankle osteoarthritis with larger sample sizes in Canada may help to reduce the uncertainty in decision-making.

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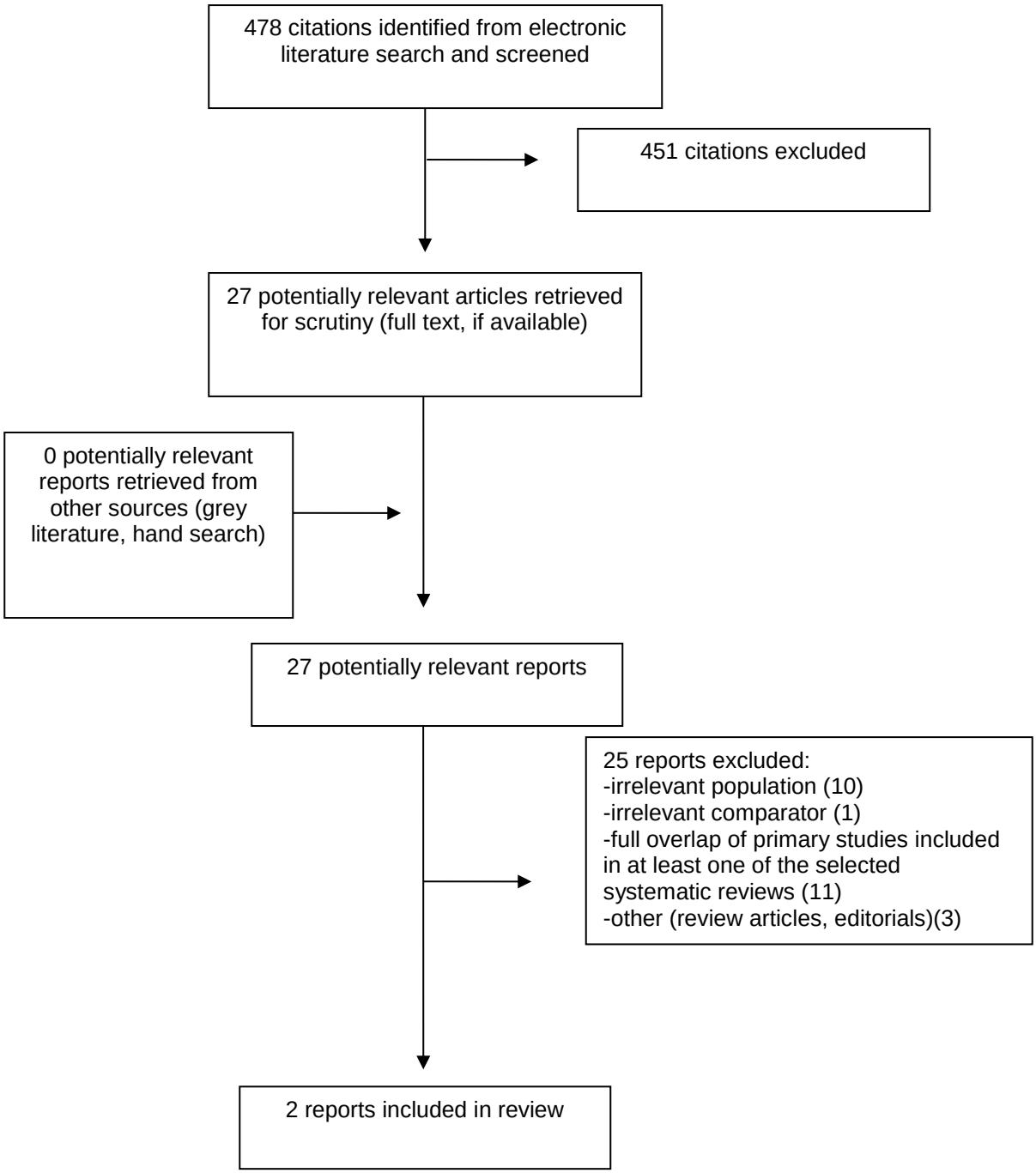
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Hip				
Leite, Amadera, and Buehler 2018, Brasil[10]	9 RCTs listed in the Results (however 8 RCTs reported in the Abstract) Databases searched: PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov database, and specific journals Up to March 2017 Inclusion criteria: "*(1) randomized controlled trials (RCTs); (2) evaluation of any viscosupplementation regimen in patients with hip osteoarthritis, compared with any other active or placebo intra-articular injection; and (3) presentation of at least 1 of the following outcomes: pain, disability, quality of life, Outcome Measures in Rheumatoid Arthritis Clinical TrialseOsteoarthritis Research Society International (OMERACT-OARSI) Responder Index,20 or adverse events (AEs)*" (*p*575)	1,164 in total in the Study characteristics table, 942 in 6 RCTs eligible for the inclusion criteria of this report (however 807 patients reported in the abstract) Mean age: 53 to 73 years Sample sizes: 42 to 357	Intra-articular injections for hip osteoarthritis HA [1, 2, or 3 injections; 0.5 to 90 megadalton(molecular weight); 6 brands] versus any: placebo (n = 4); platelet-rich plasma (PRP) (n = 3); methylprednisolone (n = 3); and mepivacaine (n = 1)	Primary outcome: pain (all measurement tools accepted) Secondary outcomes: disability, quality of life, Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) Responder Index (a scale based on measures of pain, function, and patient's global assessment),[11] and adverse events Pain measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) meta-analyzed Follow-up lengths: 1 to 12 months
Ankle				
Vannabouathong et al. 2018, Canada[9]	27 studies (20 observational and 7 RCTs)	1,085 patients with ankle osteoarthritis (22 studies), rheumatoid	Intra-articular Injections for ankle arthritis compared with each other:	Pain, function, stiffness, quality of life, or disease-specific indices, adverse events, patient

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Databases searched: Medline, Embase, and Cochrane Library databases Search dates not available in the publication Inclusion criteria: "*Case series, cohort, and randomized controlled trials (RCTs) evaluating an intra-articular therapy for the treatment of ankle arthritis were eligible for this review. The intra-articular treatments included were corticosteroids, hyaluronic acid (or viscosupplementation), platelet-rich plasma, and mesenchymal stem cells. At least 1 efficacy (pain, function, quality of life, and patient satisfaction) or safety (adverse events and pain medication consumption) outcome had to be reported*" (*p*1141)	arthritis, or hemophilic arthropathy 165 patients eligible for this report Range of mean ages: 29.3 to 61.9 years Range of sample sizes: 4 to 100	corticosteroids (n = 4), hyaluronic acid (HA) (n = 19), platelet-rich plasma (PRP) (n = 3), and mesenchymal stem cells (MSC) (n = 1) Characteristics of the interventions (including dosage, brand names, and molecular weights) not described	satisfaction, and tolerability outcomes Measurement tools including visual analog scale, Short-Form 36, Ankle Osteoarthritis Scale, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), American Orthopaedic Foot & Ankle Society score, Foot and Ankle Outcome Score, Japanese Society for Surgery of the Foot, Self-Administered Foot Evaluation Questionnaire, Foot and Ankle Disability Index, acetaminophen consumption, range of motion Only Ankle Osteoarthritis Scale (based on measures of pain and disability)[13] meta-analyzed Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a scale based on measures for pain, stiffness, and functional limitations[14] Follow-up length: 2 to 30 months

AE = adverse event; MSC = mesenchymal stem cells; OMERACT-OARSI = Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International; PICO = population, intervention, comparator, and outcome; PRP = platelet-rich plasma; RCT = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2 checklist[7]

Strengths	Limitations
Leite, Amadera, and Buehler, 2018[10]	
- PICO criteria described - Review protocol published *a priori* - Selection of study design described - Comprehensive literature search - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with published tools - Appropriate statistical methods used for meta-analysis - Potential impact of the risk of bias in the included studies on the results assessed - Risk of bias in the included studies considered when interpreting the results - Heterogeneity in the results discussed - Publication bias assessed	- Study selection in duplicate not reported - Excluded studies not listed - Sources of funding of the included studies not reported - Review authors' competing interests not reported
Vannabouathong et al., 2018[9]	
- PICO criteria described - Selection of study design described - Comprehensive literature search - Included studies described - Risk of bias in the included studies assessed with published tools - Appropriate statistical methods used for meta-analysis - Potential impact of the risk of bias in the included studies on the results assessed - Risk of bias in the included studies considered when interpreting the results - Heterogeneity in the results discussed - Study selection in duplicate - Sources of funding of the included studies reported - Review authors' competing interests reported	- Excluded studies not listed - Review protocol not published *a priori* - Data extraction in duplicate not reported - Publication bias not assessed

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Leite, Amadera, and Buehler, 2018[10]	
Hip osteoarthritis HA versus placebo (4 RCTs) Pain at 3 months - Standardized mean difference = -0.06 (95% CI, -0.38 to 0.25; *P* = 0.69) Adverse events - Risk ratio = 1.21 (95% CI, 0.79 to 1.86; *P* = 0.38) HA versus methylprednisolone (3 RCTs) Pain at 1 month - Standardized mean difference = 0.02 (95% CI, -0.18 to 0.22; *P* = 0.85) Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) Responders Index at 1 month - Risk ratio = 0.44 (95% CI, 0.10 to 1.95; *P* = 0.28) Adverse events - Risk ratio = 1.21 (95% CI, 0.79 to 1.87; *P* = 0.38)	"*We do not recommend viscosupplementation for hip osteoarthritis. Compared with placebo, data show scarce evidence of its efficacy up to 3 months, and suggest no difference at 6 months*" (*p*56) HA versus placebo (4 RCTs) Pain at 3 months - "*very low evidence that HA is not superior to placebo for pain at 3 months*" (*p*56) Adverse events - "*high evidence that it is not superior*" (*p56*) HA versus methylprednisolone (3 RCTs) Pain at 1 month - "*high evidence that HA is no different from methylprednisolone*" Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) Responders Index at 1 month - "*low evidence that HA is no different from methylprednisolone*" (*p*56) Adverse events - "*high evidence that HA is no different from methylprednisolone*"
Vannabouathong et al., 2018[9]	
Ankle osteoarthritis Hyaluronic acid versus saline Ankle Osteoarthritis Scale scores (3 RCTs, 109 patients) - Significantly improved with HA over saline at 6 months - Mean difference = 12.47 points (95% CI 1.18 to 23.77, P = 0.03) - 2 RCTs (Cohen 2008 and Salk 2005) using a 5-injection regimen of Hyalgan: HA improved pain, function, and stiffness (AOS and WOMAC) up to 26 weeks - 1 RCT (DeGroot et al.; single injection): no differences on the VAS, AOS, and AOFAS between saline and a single injection of Supartz at 12 weeks - Sensitivity analysis by removing the DeGroot et al.: mean difference in the Ankle Osteoarthritis Scale scores statistically significant in favor of HA (MD = 14.23, 95% CI 2.55 to 25.90, *P* = 0.02; I^2 = 1%)	"*Evidence from small trials favors HA and PRP injections for the treatment of pain associated with ankle osteoarthritis*" (*p*1141)

AOFAS = American Orthopaedic Foot & Ankle Society; AOS = Ankle Osteoarthritis Scale; CI = confidence interval; CS = corticosteroid; HA = hyaluronic acid; MD = mean difference; MSC = mesenchymal stem cells; OA = osteoarthritis; PRP = platelet-rich plasma; RCT = randomized controlled trial; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Appendix 5: Overlap between Included Systematic Reviews

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Leite 2018[10] (n = 9) Hip	Vannabouathong 2018[9] (n = 27) Ankle
Atchia 2011*	X	
Battaglia 2013	X	
Brander 2016*	X	
Dallari 2016	X	
Di Sante 2016*	X	
Migliore 2009	X	
Qvistgaard 2006*	X	
Richette 2009*	X	
Spitzer 2010*	X	
Sarkin 1974		X
Lopes 2008		X
Fox 2013		X
Furtado 2017		X
Fernandez-Palazzi 2002		X
Salk 2005#		X
Sun 2006#		X
Carpenter 2008#		X
Cohen 2008#		X
Karatosun 2008#		X
Luciani 2008#		X
Witteveen 2008#		X
Mei-Dan 2010#		X
Witteveen 2010#		X
Sun 2011#		X
Carulli 2012#		X
DeGroot 2012#		X
Lucas 2013#		X
Witteveen 2013#		X
Han 2014#		X

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Leite 2018[10] (n = 9) Hip	Vannabouathong 2018[9] (n = 27) Ankle
Sun 2014#		X
Bossert 2016#		X
Murphy 2017#		X
Angthong 2013		X
Fukawa 2017		X
Repetto 2017		X
Emadedin 2015		X

*patients with hip osteoarthritis treated with hyaluronic acid, compared to those treated with steroid or placebo; relevant to this report, #patients with ankle osteoarthritis treated with hyaluronic acid, compared to those treated with steroid or placebo, relevant to this report

Appendix 6. Characteristics of outcome measures

Table 6: Characteristics of outcome measures

Measures	Abbreviations	Validation	Validation populations	Components or domains
Ankle Osteoarthritis Scale	AOS	Domsic and Saltzman 1998[13]	Non-patients	Pain and disability
Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International Responder Index	OMERACT-OARSI Responder Index	Pham et al. 2004[11]	Osteoarthritis patients	Pain, function, and patient's global assessment
Western Ontario and McMaster Universities Osteoarthritis Index	WOMAC	Bellamy et al. 1988[15]	Patients with osteoarthritis of the hip or knee	Pain, stiffness and physical function

Appendix 7: Additional References of Potential Interest

Reviews without systematic literature searches

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