Efficacy and safety of Intra-articular Injections with Hyaluronic Acid in the treatment of osteoarthritis: Protocol for a meta-analysis of randomised placebo-controlled trials

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ABSTRACT

Introduction: Osteoarthritis (OA) is the most common musculoskeletal condition and is a major cause of pain, disability and loss of quality of life. Intraarticular injections of hyaluronic acid (HA) are widely used in the management of osteoarthritis when other treatments as NSAID come to term or have to severe adverse events. The rationale of intra-articular HA injection is to restore the viscosity of the synovial fluid. There are divergent opinions of effect and possible adverse events of HA. Therefore we will provide a systematic review with meta-analysis of the efficacy and safety of viscosupplementation with hyaluronic acid.

Methods and analysis: A systematic review with meta-analysis of randomised or quasi-randomised, controlled trials of viscosupplementation with HA (vs. sham or with non-intervention control) will be considered eligible for inclusion in the meta-analysis. Changes in pain and serious adverse events will be primary endpoint and secondary endpoints will be changes in function and discontinuation due to adverse events. Electronic searches will be performed in MEDLINE, EMBASE, Web of Science and The Cochrane Library, along with manually searches of reference list of specialist journals and conference proceedings. Furthermore unpublished trials will be searched in clinicaltrials.gov and clinicaltrialregister.eu. The primary meta-analysis will be performed using random effects models owing to expected intertrial heterogeneity. Dichotomous data will be analysed using risk difference and continuous data using weighted mean differences, both with 95% CIs.

Ethics and dissemination: The study will evaluate the potential effect and adverse events of viscosupplementation with hyaluronic acid to the clinical management of patients with Osteoarthritis.

Results: The study will be disseminated by peer-review publication.

Protocol registration: PROSPERO CRD42014007284.

INTRODUCTION

Description of the condition

Musculoskeletal conditions are one of the most common causes of severe long-term pain and impaired physical function. These conditions are diverse (1).

Osteoarthritis (OA) is the most common musculoskeletal condition and is a major cause of pain, disability and loss of quality of life. The prevalence of OA increases with age due to the irreversibility of the condition, with approximately 9.6% of men and 18.0% of women aged ≥60 years having symptomatic osteoarthritis (1). Obesity, injuries in the joint, previous surgery and occupational bending and lifting are the among risk factors for OA (1-3).

OA most commonly affects knees, hips, hands and spine (2). The greatest population impact is seen in lower limb disabilities (4). OA affects all structures in the joint, with loss of articular cartilage within synovial joints, leading to hypertrophy of bone, capsular thickening and changes in the synovial fluid. OA is clinically characterized by joint pain, weakness of periarticular muscles, limitation in movement, crepitus, tenderness, effusions and local inflammation (2, 3).

Management of osteoarthritis

Currently OA treatment aims to relieve pain symptoms in different ways (5). The available treatments can roughly be categorized in non-pharmacological intervention, pharmacological treatment, invasive/surgical intervention (including intra-articular injections, lavage and arthroplasty) and complementary alternative management (2). OA is to a great extent treated with analgesics including non-steroid anti-inflammatory drugs (NSAIDs). Unfortunately these treatments are not effective for all patients and have well-known adverse events (5). For patients where pain is not being alleviated by the NSAIDs (6), intra-articular injection, e.g. corticosteroid, is taken into consideration. This is by some considered an effective treatment with some characteristic adverse effects (3).

Hyaluronic Acid (HA) consists of natural high-viscosity mucopolysaccharides with alternating beta (1-3) glucuronide and beta (1-4) glucosamine bonds. HA is naturally occurring in synovial fluid acting as a lubricant and shock absorber, and the elastoviscosity of the synovial fluid diminishes in the development of OA (7, 8).

Viscosupplementation with HA is believed to be an effective therapeutic modality where the synovial fluid is replaced or supplemented by a fluid with higher viscosity than the one present (7). HA is injected intra-articularly to improve the biomechanical function of the joint. It is a natural component of the synovial fluid and an important contributor to the joint health. In OA there is a

decrease in both the concentration and the molecular weight of HA, as well as a reduction of the viscosity of the synovial fluid. The rationale of intra-articular HA injection is to restore the viscosity of the synovial fluid (7-9). There are divergent opinions of effect and possible adverse events of HA (9).

Meta-Analyses evaluating viscosupplementation

In order to promote evidence-based research (10-13), we initially explored the research field on viscosupplementation in OA, by including a quasi systematic approach to locate any systematic reviews available in Medline via PubMed from dates 01.10.2013 using a filter previously described (5) combined (=AND) with various terms for viscosupplementation:

- meta-analys*[pt] OR meta-analys*[ti] OR metaanalys*[ti] OR meta-regress*[tiab] OR metaregress*[tiab] OR Consensus[mh] OR "Evidence-Based Medicine"[mh] OR "Delphi Techniques"[mh]
- Osteoarthritis[mh] OR Osteoarthritis[ti]
- "Viscosupplements"[Ti] OR "Viscosupplements"[mh] OR "Viscosupplementation"[Ti] OR "Viscosupplementation"[mh] OR "Hyaluronic Acid"[Ti] OR Hylan[Ti]

Two individual reviewers searched Medline via Pubmed without language restrictions. Last search was carried out on 1 October 2013. Two reviewers evaluated the reports independently for eligibility. Disagreement was resolved by consensus or with third reviewer RC.

From this search we identified 26 references and considered 16 to be potentially eligible, from these 14 systematic reviews/meta-analyses comparing viscosupplementation with placebo or an active control group for the treatment of OA was selected. Furthermore 1 systematic review comparing viscosupplementation with placebo or an active control group for the treatment of OA was identified by specialist in the field.

Methodological quality of systematic reviews and quality of the evidence

Several tools have been created to assess systematic review quality (14-17). We applied the measurement tool for assessing the methodological quality of systematic reviews known as the AMSTAR tool, applying a yes/no/can't answer/not applicable score to eleven relevant domains of review methodology.

Table 1 illustrates the score for each domain and the evaluated AMSTAR score.

Table 2 illustrates narratively the conclusions in each of the reviews and the total AMSTAR score.

Table 1

AMSTAR	Miller 2013	Chang 2013	Rutjes 2012	Colen 1 2012	Colen 2 2012	Bannuru 2011	Divine 2007	Dagenais 2006	Medina 2006	Bellamy 2006	Modawal 2005	Arrich 2005	Wang 2004	Lo 2003	Espallargues 2003
Item 1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1
Item 2	0	0	1	1	1	1	0	0	1	0	0	0	1	0	1
Item 3	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1
Item 4	0	1	1	0	0	1	0	0	0	1	0	0	0	1	1
Item 5	0	1	1	1	0	1	0	0	1	0	1	1	1	1	0
Item 6	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1
Item 7	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1
Item 8	0	0	1	0	0	1	1	0	0	1	1	1	1	1	1
Item 9	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0
Item 10	1	1	1	0	0	0	0	0	0	0	1	1	1	1	0
Item 11	1	0	1	1	1	1	0	1	0	1	0	1	1	1	1
Total	**6**	**8**	**11**	**7**	**6**	**10**	**3**	**1**	**4**	**7**	**8**	**9**	**10**	**10**	**8**

Table 2

Author year	Title	AMSTAR score	Conclusion
Miller et al. 2013	US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials.	6	We conducted the first systematic review and meta-analysis of US-approved HA products on knee OA symptoms. Overall, we conclude that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee OA.
Chang et al. 2013	Effectiveness of intra-articular hyaluronic acid for ankle osteoarthritis treatment: a systematic review and meta-analysis.	8	Intra-articular HA administration can significantly reduce pain in ankle OA compared with the condition before treatment, and it is likely superior to reference therapy. We recommend using multiple doses with an appropriate injection volume to achieve maximum effectiveness.
Rutjes et al. 2012	Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis.	11	We conclude that the benefit of viscosupplementation on pain and function in patients with symptomatic osteoarthritis of the knee is minimal or non-existent. Because of increased risks for serious adverse events and local adverse events, the administration of these preparations should be discouraged.
Colen et al. 2012	Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products.	7	In the future it will be important to determine the exact mechanism of action of placebo as this may give us an idea of how to treat osteoarthritis more efficiently. Due to the limitations of this review (follow-up of the different HA products to determine which product(s), or which molecular weight range, concentration, just 3 months and large heterogeneity of the included studies), it is also important to compare the different HA products to determine which product(s), or which molecular weight range, concentration, or volume of HA is the best option to treat osteoarthritis. Our recommendation is to start large (multicentre) RCTs to give us more evidence about the efficacy of the different HA products.
Colen et al. 2 2012	Hyaluronic Acid for the Treatment of Osteoarthritis in all Joints Except the Knee	6	After performing a systematic review using a rigid methodology with the objective to pool the outcome data of included studies, we have to conclude that there is evidence of improvement compared with baseline of intra-articular HA treatment regimens. On the other hand, there is limited evidence of improvement comparing HA with placebo and no evidence that intra-articular treatment with HA is better than CS or other conservative therapies.
Bannuru et al. 2011	Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis.	10	IAHA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks. On the other hand, the peak effect size (0.48; 0.28, 0.65), is greater than published effects from other OA analgesics [acetaminophen (ES ¼ 0.13; 0.04, 0.22); NSAIDs (ES ¼ 0.29; 0.22, 0.35); COX-2 inhibitors (ES ¼ 0.44; 0.33, 0.55)]. An effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. Thus, its properties could have utility for certain clinical situations, or in combination with other therapies.
Divine et al. 2007	Viscosupplementation for knee osteoarthritis: a systematic review	3	Based upon this systemic review, we conclude that although they differ in several methods for determining individual trial quality, each of the five meta-analyses presented offer scientifically sound Level 1 evidence to support the efficacy of HA use in select patients with OA.
Dagenais et al. 2006	Intra-articular hyaluronic acid (viscosupplementation) for knee osteoarthritis.	1	Reviews and practice guidelines show that HA is most suitable for patients <65 years old with mild to moderate pain, effusion, and radiographic findings, and in those for whom other approaches are contraindicated, or have failed. Demand for IIA will likely be high, although eligibility criteria will decrease the size of the potential market. The repeated office visits required for administration by IA injection will increase demand for services from primary care physicians, rheumatologists, physiatrists, orthopaedists, and specialists in rheumatic disease. The use of HA will also likely increase the demand for radiological and laboratory testing.
Medina et al. 2006	Knee osteoarthritis: should your patient opt for hyaluronic acid injection?	4	Based on this meta-analysis, we cannot conclude that hyaluronic acid performs better than saline placebo for a reduction of pain or disability on the WOMAC. Some indication may be warranted for reduction in stiffness. It is notable that hyaluronic acid injection and saline placebo groups both experienced an improvement in pain, stiffness, and disability scores on the WOMAC.
Bellamy et al. 2006	Viscosupplementation for the treatment of osteoarthritis of the knee.	7	In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events. In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.
Modawal et al. 2005	Hyaluronic acid injections relieve knee pain.	8	Intra-articular viscosupplementation was moderately effective in relieving knee pain in patients with osteoarthritis at 5 to 7 and 8 to 10 weeks after the last injection but not at 15 to 22 weeks.
Arrich et al. 2005	Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis.	9	According to the currently available evidence, intra-articular hyaluronic acid has not been proven clinically effective and may be associated with a greater risk of adverse events. Large trials with clinically relevant and uniform end points are necessary to clarify the benefit–risk ratio.
Wang et al. 2004	Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials.	10	This meta-analysis confirmed the therapeutic efficacy and safety of intra-articular injection of hyaluronic acid for the treatment of osteoarthritis of the knee. Additional well-designed randomized controlled trials with high methodological quality are needed to resolve the continued uncertainty about the therapeutic effects of different types of hyaluronic acid products on osteoarthritis of the knee in various clinical situations and patient populations.
Lo et al. 2003	Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis.	10	Intra-articular hyaluronic acid has a small effect when compared with an intra-articular placebo. The presence of publication bias suggests even this effect may be overestimated. Compared with lower-molecular-weight hyaluronic acid, the highest-molecular-weight hyaluronic acid may be more efficacious in treating knee OA, but heterogeneity of these studies limits definitive conclusions.
Espallargues et al. 2003	Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: a systematic review.	8	There is good quality scientific evidence showing that Hylan G-F 20 is a safe and well-tolerated therapy providing a short-term decrease of the pain symptoms while improving joint function, the delay of the need for knee replacement as well as the durability of the effect over the longer term have only been demonstrated in non-controlled clinical series. The available evidence is not sufficient to reach firm conclusions on the effect of multiple courses of intra-articular injections of Hylan G-F 20 on health outcomes.

Why it is important to do this review

Existing research and guidelines on management of OA disagree on the potential benefit of HA resulting in low strength of recommendation (5). In 2010, the 'Osteoarthritis Research Society International' (OARSI), reported superior effect size of intra-articular HA compared to intra-articular corticosteroids at 5-13 weeks, but no effect after 14 weeks following completion of treatment. No serious adverse events were reported. OARSI suggests publication bias and no evidence for significant pain relief when analyses were restricted to high quality studies (18). In 2012, the American College of Rheumatology, (ACR), '*Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee*' makes no recommendation regarding the use of intra-articular HA while conditionally recommending intra-articular corticosteroids (19). According to the quality of the existing systematic reviews (see Table 1) the methodological differences across meta-analyses could explain some of the discrepancies.

Objectives

The aim is to estimate the efficacy and safety of HA in subjects with symptomatic osteoarthritis vs. sham or non-intervention control.

METHODS

Protocol and registration

Our protocol is registered on PROSPERO (CRD42014007284); We will follow this protocol through all review steps. All steps will be performed according to the MECIR recommendations, and the subsequent manuscript will be reported according to the '*Preferred Reporting Items for Systematic reviews and Meta-Analyses*' (PRISMA) statement (20).

Eligibility criteria

Types of studies

Only randomised or quasi-randomised, controlled trials which compare viscosupplementation with sham or with non-intervention control will be considered eligible for inclusion in the meta-analysis. No language restrictions will be applied.

Types of participants

We will include studies if the authors report that participants are clinically diagnosed with osteoarthritis according to ACR criteria (21). We have no restriction concerning race or sex, but will only include studies with participants above 18.

Types of interventions

We will include studies, which have used any types of viscosupplementation with all types of HA. There will be no restrictions on dosage; molecular weight, number of injections per cycle, or follow-up duration. Studies without an "inactive" control group will be excluded. Studies where viscosupplementation with HA is used following a surgical procedure will not be included.

Types of outcome measures

As primary outcomes we will use pain and serious adverse events. As secondary outcomes we will use physical function and discontinuation due to adverse events.

Primary outcomes

Pain: If data is reported on more than one pain scale we will use the prioritised list of patient-reported outcomes for systematic reviews and meta-analysis developed by Juhl et al. presented below (22).

1. WOMAC pain subscale (Likert/100mm)
2. Pain during activity (VAS)
3. Pain during walking (VAS)
4. Global knee pain (VAS)
5. Pain at rest (VAS)
6. SF-36 (bodily pain (BP) subscale)
7. HAQ (pain subscale), Lequesne algofunctional index (pain subscale), AIMS (pain subscale), Knee-Specific Pain Scale (KSPS), McGill Pain Questionnaire (pain intensity), ASES (pain subscale), SES (Schmerzempfindungsskala)
8. Pain at night (VAS), pain during activity (NRS), pain on walking (NRS), number of painful days (days)

Serious adverse events: Adverse events categorized as a serious deterioration in health either resulting in: patient hospitalization, prolongation of existing hospitalization, permanent impairment of body structure or body function, life-threatening illness or injury, cognital abnormality of offspring or death (23).

Secondary outcomes

Physical function: If data is reported on more than one physical function scale we will use the prioritised list of patient-reported outcomes developed by Juhl et al. for systematic reviews and meta-analyses presented below (22).

1. WOMAC subscale function (Likert/100mm)
2. SF-36 (subscale physical function (PF))
3. Physical composite score (PCS) based on SF-36, SF-12, or SF-8
4. HAQ (disability subscale), PDI (pain disability index), ASES (disability subscale)

Discontinuation due to adverse events: Any adverse events that leads to withdrawal.

Time point

We will use data from the outcome assessment conducted 3 months (range: 8-16 weeks) following completion of the intervention as the time point of primary interest. When data are available, we will also extract the effects at long-term follow-up defined as 6 months from baseline (range: 4-7 months).

Searches and selection of trials and meta-analyses

We will follow the Cochrane Handbook for Systematic review and meta-analysis in the literature search and selection (24). Studies will be identified by searching bibliographic databases, including MEDLINE via Pubmed from 1966, EMBASE via Ovid from 1974, Web of Science via Web of Knowledge from 1960 and the Cochrane Library from 1998, all up to march 1st 2014. The limitation human will be imposed where possible.

Manual searches including scanning of reference lists of identified systematic reviews will be performed. We will search specialist journals; 'Osteoarthritis and Cartilage' and 'Arthritis and Rheumatology', and conference proceedings; OARSI, ACR and EULAR from 2012 to 2014. Unpublished trials will be sought by correspondence with experts in the field of osteoarthritis and/or viscosupplementation and by searching in clinicaltrials.gov and the http://apps.who.int/trialsearch/. No language, publication date, or publication status restrictions will be imposed.

Eligibility assessment will be performed in a standardised manner by to independently reviewers (MJ, HB). Disagreement will be solved by consensus or help from a third reviewer (RC).

Duplicate records will be removed from the selected references. Two independent review authors (MJ, HB) will screen identified titles and abstracts to identify potentially relevant studies. Full text articles will be obtained and two independent reviewers (MJ, HB) will screen for eligibility and

decide on their inclusion. Disagreement will be solved by consensus or help from a third reviewer (RC). A record of agreement and reasons for excluding studies will be kept. If multiple reports relating to the same trial are detected, only the original data or report with data of relevance will be used.

Search terms

Search terms related to osteoarthritis

osteoarthritis OR osteoarthri* OR osteo arthri* OR osteoarthro* OR arthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro*

Search terms related to hyaluronic acid/viscosupplementation

hyaluronic acid OR viscosupplement* OR viskosupplement* OR visco supplement* OR visko supplement* OR Adant* OR arthrum* OR artz* OR BioHy* OR biotty* OR Durolane* OR euflexxa* OR gel200* OR gel-200* OR GelOne* OR Gel-One* OR GF-20* OR go-on* OR healon* OR HYADD* OR hya-ject* OR hyalan* OR hyalart* OR hyalectin* OR hyalgan* OR hyaluron* OR hy-gag* OR hylan* OR monovisc* OR nrd101* OR nrd 101* OR nuflexxa* OR orthovisc* OR ostenil* OR polireumin* OR RenehaVis* OR replasyn* OR supartz* OR suplasyn* OR synov-hyal* OR synvisc*

Search terms related to design

randomized OR randomised OR controlled OR placebo* OR random OR control group OR double blind OR doubleblind OR single blind OR singleblind

Risk of bias in individual studies

Quality assessment in the included studies will be performed using the risk of bias tool recommended by the Cochrane Handbook for Systematic review and meta-analysis chapter 8 (24). Two reviewers (MJ, HB) will independently assess specific domains. Each of those key domains of methodological quality will be categorised as Adequate (low risk of bias), Unclear, or Inadequate (high risk of bias). Disagreements will be solved by discussion and if agreement cannot be reached, it will be decided by third reviewer (RC).

The risk of bias quality assessment will be pilot tested on ten randomly selected eligible studies.

- **Sequence generation**

Adequate will be applied if a random approach in the sequence generation process referred to a random number table, a random computer generated number, coin tossing, drawing of lots, shuffling cards, or throwing dice is described.
Inadequate will be applied if a sequence generation process referred to as date of birth, inclusion or admission, or record number of clinic/hospital is described
Unclear will be applied if the information about the process is insufficient to make the judgement.

- **Allocation concealment**

Adequate will be applied if central allocation is used (including web based or pharmacy controlled randomization). if there are used sequentially numbered drug containers of identical appearance or if sequentially numbered, opaque, sealed envelopes is provided. Inadequate will be applied if assignment envelopes without appropriate safeguards is provided (e.g. unsealed or non-opaque or not sequentially numbered).
Inadequate will be applied if a predictable assignment i performed (e.g. date of birth, alternation, open random allocation schedule, unsealed envelopes or any other explicitly unconcealed procedure)
Unclear will be applied if allocation concealment is not reported or insufficient information to make the judgement.

- **Blinding**

Adequate will be applied if the participants, personnel and outcome assessors are ensured complete lack of knowledge of treatment allocation; If the provision of indistinguishable products in the active and control group are provided; If the outcome measures are not assumed to be affected by the lack of blinding or if safety outcomes is assumed not to be affected by the lack of blinding.
Inadequate will be applied if there is no blinding or incomplete blinding of participants, personnel and outcome assessors; if self-reported pain and disability outcomes are assumed to be affected by the lack of blinding or if blinding is attempted, but it is likely that the blinding could have been broken.
Unclear will be applied if insufficient information of blinding is reported.

- **Incomplete outcome data addressed**

Adequate will be applied if all randomized patients were included in the group they were originally allocated to, regardless of their adherence to the study protocol, in an intention to treat analysis (ITT); if there is no missing data; if the missing data is not related to outcomes (e.g emigration); if

missing data is evenly distributed across groups and of the similar reasons across groups; if missing data is imputed using appropriate methods (e.g. multiple imputation analysis and worst case analysis).
Inadequate will be implied if reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; if 'As-treated' (per protocol) analysis done with substantial departure of the intervention received from that assigned at randomization or if potentially inappropriate application of simple imputation (e.g."last observation carried forward").
Unclear will be applied if insufficient reporting of attrition/exclusions to permit judgement of adequate or inadequate (e.g. number randomized not stated, no reasons for missing data provided).

- **Selective outcome reporting**

Adequate will be applied if pre-specified outcomes are reported as described in the protocol (For studies published after 1st July 2005, we will screen http://apps.who.int/trialsearch/ and www.clinicaltrials.gov for the a priori trial protocol); if a protocol is not available but all expected outcomes are reported, independently of the statistical significance of the results; if prespecified outcome listed in the Methods section are the same as those reported in the Result section (with distinction made between primary and secondary outcomes).
Inadequate will be applied if not all of the study's pre-specified primary outcomes have been reported; if one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; if one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); if one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis or if the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Unclear will be applied if insufficient information to reach a judgement (e.g. study protocol not available and no outcome prespecified, with distinction made between primary and secondary outcomes in the Methods section).

- **Other potential source of bias**

Industry supported trials:
Adequate will be applied if the trial setting is supported by a non-profit foundation or similar organization, where a positive outcome will not have economically benefits.

Inadequate will be applied if the trial setting is supported by a for-profit organization or similar organization, where a positive outcome will have economically benefits or if funding is not reported.
Single-centre vs. Multi-centre trials:
Adequate will be applied if the trial is designed as a multi-centre trial.
Inadequate will be applied if designed as a single-centre trial.

Each RCT will be assigned an overall Risk of Bias term.

Low Risk of bias will be applied when the study follows the protocol e.g. available in clinicaltrial.gov or are considered to have minor limitations that are considered not to have influence on the estimate in the above listed Risk of Bias; concerning sequence generation, allocation concealment, blinding, incomplete outcome data addressed and selective outcome reporting.

High Risk of Bias will be applied when no protocol is available or if serious limitations in the above listed Risk of Bias

Unclear Risk of Bias will be applied if there are uncertainty concerning the above listed Risk of Bias.

Data collection process and data items

Data will be extracted using a standardised form. The data extraction sheet will be pilot tested on ten randomly selected eligible studies, and refined accordingly. Two reviewers (MJ, HB) will independently extract data from the included trials. Extracted data will be entered into Review Manager (RevMan; Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Disagreements will be solved by discussion and if agreement cannot be reached, it will be decided by third reviewer (RC).
If incomplete data is detected in a study, the author of the primary study will be contacted to obtain additional data.
The following data will be extracted by default:

- General study information: Study ID; main author, publication year, title, contact author, publication source, publication status, country of main author and trial sponsors.
- Characteristics of the methods: Study design (e.g parallel group, 2x2 factorial design, etc.), number of participants (randomised/analysed), study duration from baseline to end of follow-up, use of sham/control.

- Characteristics of the intervention: Joint (knee, hip and other), type of HA (manufacturer/druglabel); dose; average molecular weight, molecular structure; number of cycles; and number of injections. Ultrasound monitored injected/not ultrasound monitored injections.
- Internal validity: classification of studies according to risk of bias (see above): randomisation procedure, concealment of allocation, blinding of participants/personnel, blinding of outcome assessors, handling of missing data with a proper intention-to-treat analysis (ITT) strategy, type and source of funding and foundations, and type of study (single- or multicentre trial).
- External Validity: combined baseline characteristics of the intervention and control groups: trial inclusion criteria, exclusion criteria, diagnostic criteria, average age, number of females sex (no [%]) and average duration of symptoms.
  Outcome measures: efficacy assessed as follow-up data, in available outcome measure in/of pain, disability and exploratory outcomes
- Safety outcomes will be assessed as the number of serious adverse events and withdrawal due to adverse events.

Results will be extracted as the ITT population where possible.

In studies with more than one active intervention arm, the placebo group will be split up to avoid inflated standard errors as recommended in Cochrane Handbook Chapter 16 (24).

For continuous outcomes changes in pain, function and physical performance will be extracted as follow-up data with standard deviations on the basis of standard errors, confidence intervals (CI) or P values for differences in means (MD) between the experimental group and the control group as recommended by The Cochrane Handbook (24).

When extracting data we will use a prioritised list presented below. If both follow-up data and change from baseline are available both will be extracted. If follow-up data in mean values are unavailable, change score will be extracted and these combined (24, 25).

1. Follow-up data
2. Change from baseline

Safety outcomes will be extracted as dichotomous data (patients with serious adverse events and patients withdrawing from the study due to adverse events) according to the numbers in each of the two outcome categories in each of the intervention groups (the numbers needed to fill in the four boxes nE, NE, nC, NC) and entered into a Microsoft Excel spreadsheet as the numbers with the outcomes and the total sample sizes for the two groups.

Data synthesis and analysis

Measures of treatment effect (summary measures)

The results of the studies will be analysed using Review Manager (RevMan 5.2), Stata V.12 (Stata Corp, Texas, USA) and SAS software (PROC MIXED version 9.2; SAS Institute Inc., Cary, NC, USA). The primary meta-analysis will be performed using random effects models owing to an expected intertrial heterogeneity.

Continuous data will be expressed as the standardized mean difference (SMD) and dichotomous data will be expressed as relative risk (RR) with their respective confidence intervals (CI).

We have prespecified a minimal clinical important difference approximated to an effect size of 0.2 according to Cohen (26).

Negative effect sizes will indicate a beneficial effect (e.g. reduction in pain) of the experimental intervention relative to the control.

Assessment of heterogeneity

In addition to reviewing forest plots the intertrial heterogeneity will be expressed using the inconsistency I^2 index, which can be interpreted as the percentage of total variation across several studies due to heterogeneity. An I^2 value from 0% to 40 % might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable heterogeneity (24). In the case of substantial heterogeneity, the data will be explored further, including sub-group analyses, in the attempt to explain the heterogeneity.

Sensitivity analysis and risk of bias across studies

Stratified analysis will be performed on the primary outcomes pain and serious adverse events.

The following subgroup analyses are pre-specified in order to explore possible clinical differences between effects sizes:

- Risk of bias analysis (24)
- Type of sham/control intervention
- Single-centre vs. multi-centre trial
- Publication status
- Funding
- Number of cycles and injections

- Follow-up duration
- Molecular weight
- Molecular structure
- Manufacturer/druglabel
- Joint (knee, hip, other [incl. ankle, shoulder, hand, tendi-mandibular-joint])

Furthermore small study bias analysis will be performed.

On adverse events we will estimate the Number Needed to Treat in order to harm a patient (NNT[H]), with a 95% CI on the basis of the combined RR value, applying the overall event rate in the placebo/sham groups as a proxy for baseline risk.

Additionally we will estimate the Number Needed to Treat for an additional beneficial outcome (NNT[B]) with a 95% CI on the basis of a (log) odds ratio transformed from SMDs of continuous data (24).

Summary of findings

We will include a 'Summary of findings' table which will provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* and an overall grading of the evidence related to each main outcome, using the GRADE approach (24).

ETHICS AND DISSEMINATION

The study will evaluate the impact (effect and adverse events) of viscosupplementation with all types of HA on osteoarthritis. Despite previous research there remain some uncertainties about the effect size and adverse events and the severity of these.

For the patients for whom non-pharmacological treatment methods are not feasible pharmacological treatment is the available option. The Public Health Care System is obliged to the patients to offer treatment possibilities that have a maximal clinically relevant effect and with a minimum of adverse events.

Consequently the results will possibly contribute to the clinical management of patients with osteoarthritis. MJ and HB will draft a paper describing the systematic review and meta-analysis and

the study will be disseminated by an international peer-reviewed journal and internally conference presentation.
We will submit the results of the trial for publication irrespective of outcome.

Contributors

HB and MJ wrote the first draft of the protocol. RC and CJ provided statistical advice for the design. RC and EMB contributed to search strategy development. All authors participated in the trial design, provided feedback on drafts of this paper and read and approved the final manuscript.

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Competing interests

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The authors declare no conflicts of interest.

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