The conservative treatment of ankle osteoarthritis

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CHAPTER 6

Conservative treatment for osteoarthritis of the ankle

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Abstract

Background: The cause of ankle osteoarthritis (OA) is mainly post traumatic. Patients are relatively young, since trauma occurs at a young age. Surgical treatment is reserved for end stage OA. Several conservative treatment options are available, however evidence of the benefits and harms of these options are lacking.

Objectives: To assess the benefits and harms of any conservative treatment for ankle OA in adults in order to provide a synthesis of the evidence as a base for future treatment guidelines.

Search methods: We searched MEDLINE (Ovid) 1946 up to 11 September 2014, EMBASE 1947 to September 2014, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO 1806 to September 2014, CINAHL 1985 to September 2014, PEDro (All years till September 2014), AMED until September 2014, ClinicalTrials.gov, Current Controlled Trials, The Dutch Register. We also screened reference lists in retrieved review articles and trials to identify potentially relevant studies.

Selection criteria: We considered randomised or controlled clinical trials investigating any non-surgical intervention for ankle osteoarthritis for inclusion.

Data collection and analysis: We used standard methodological procedures expected by the Cochrane Collaboration.

Results: Six randomised controlled trials (RCTs) were included, all analysing the use of hyaluronic acid (HA) for ankle osteoarthritis (OA). No other RCT concerning any other conservative treatment was identified.

A total of 240 patients diagnosed with ankle osteoarthritis were included in this review. Three RCT’s (109 patients) compared HA to placebo. One compared HA to exercise therapy, one compared HA combined with exercise therapy to an intra-
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For the comparison of HA to placebo, a pooled analysis of two trials (45 patients) found that the Ankle Osteoarthritis Scale (AOS) total score (measuring pain and physical function/disability) was reduced by 12% (95% CI -24% to -1%) at six months (mean difference (MD) - 12.53 (95% CI -23.84 to -1.22) on a scale of 0 to 100; Number Needed to Treat (NNT)=9) (95% CI 7 to 21), this evidence was graded as low, due to imprecision and limitations in study design. It is not known if a mean difference of 12.53 points on a 100 point scale is clinically relevant. No minimal important clinical difference is known for this score. The AOS sub score pain was decreased at 3 months (2 trials; 92 patients) (MD -1.83; 95% CI -11.33 to 7.68). The AOS sub score disability (physical function) at 3 months (2 trials; 92 patients) was decreased (MD -0.13; 95% CI -9.26 to 9.01). This evidence was graded as low, due to imprecision and limitations in study design. Radiographic joint structure changes were not investigated. For the mean quality of life at 6 months (two trials;45 patients) no exact scores were available, so meta analysis could not be performed. No serious adverse events (SAE’s) were noted and no patients withdrew because of an adverse event. The amount of adverse events (AE’S) in both groups were comparable, the Peto odds ratio (Peto OR) to have an adverse event was 2.34 higher compared to the control group (95% CI 0.45 to 12.11). This evidence is inconclusive because of a wide CI and a small amount of events. For the comparison of HA compared to exercise therapy (total of 30 patients), pain was decreased at 12 months (MD-0.70 95% CI -2.54 to 1.14) on a Visual Analogue Scale (VAS 0-10).The American Orthopedic Foot and Ankle Society score (AOFAS score) was 13.10 points (MD) higher in favour of HA (95% CI 2.97 to 23.23) on a scale of 0 to 100. This evidence was graded as low. No adverse events were found. Radiographic structure changes were not measured, no patients withdrew due to AE’s. No SAE’s were found.

For the comparison of HA injection combined with exercise therapy to an intra-articular injection of Botulinum toxin A (BoNT-A) (75 patients), the AOS pain score of the affected joint showed a decrease at 6 months (MD 0.10; 95% CI -0.42
to 0.62). The physical function (the AOS disability score) at 6 months showed a decrease (MD 0.20; 95% CI -0.34 to 0.74). The same amount of AE’s were found in both groups; HA 2/37 (5.9%), BoNT-A 2/38 (5.8%) (RR 1.03; 95% CI 0.15 to 6.91). Radiographic changes were not examined, no SAE’s were found and no patients withdrew because of an AE. The evidence was graded as low.

The RCT concerning comparing 4 different dosing schedules for HA (26 patients) showed the best median decrease in pain on walking VAS (on a scale of 0-100) for 3x1ml at 27 weeks with a median decrease of 30. Physical function, radiographic changes and quality of life were not measured. The total number of AE’s was 27%, most of them occurred at the 2 ml group (57%). No patients withdrew due to an AE and no SAE’s were noted.

Overall the quality of the evidence showed some serious limitations. The evidence was graded as low. There was a limitation in design and implementation and imprecision of the results, sample sizes were small, leading to heterogeneity in the results of the meta analysis. The risk of bias was judged to be at low risk or unclear for all the categories concerning the 3 studies used in the meta analysis. One study that was not included in the meta analysis had a high risk of bias due to lack of blinding, another an unclear risk because some patients had bilateral involvement of ankle OA which made judgement of efficacy difficult.

Authors’ conclusions: HA as treatment for ankle OA maybe safe and more effective than placebo at 6 months for pain and disability (total AOS score) based on low quality of evidence. Inconclusive results were found comparing HA to other treatments. It remains unclear which patients (age and grade of ankle OA) benefit the most from HA injections and which dosage schedule should be used. Currently, there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis.
Plain language summary

“Conservative treatment for osteoarthritis of the ankle”

Researchers in the Cochrane Collaboration conducted a review of the effect of non-surgical treatment for people older than 18 with ankle osteoarthritis in order to provide a synthesis of the evidence as a base for future treatment guidelines. After searching for all relevant studies up to September 2014, they found six studies with up to 240 people. Their findings are summarised below:

Five studies showed the results of the use of hyaluronic acid for ankle osteoarthritis compared to other treatment or to placebo (fake injection). One study was a dose finding study. Follow up was 3 to 6 months. The quality of the evidence was low, due to limitations in study design and the small amount of patients.

In people with ankle osteoarthritis: Hyaluronic acid may improve pain and function of ankle osteoarthritis at 6 months. Possible side effects might include swelling and pain of the joint, which subsides within a couple of days.

What is osteoarthritis and what is hyaluronic acid?

Osteoarthritis (OA) is a disease of the joints. When the joint loses cartilage, the bone grows to try and repair the damage. Instead of making things better, however, the bone grows abnormally and makes things worse. For example, the bone can become misshapen and make the joint painful and unstable. This can affect your physical function or ability to use your ankle.

Hyaluronic acid is a natural component of synovial fluid. Hyaluronic acid injections also called visco supplementation are gel-like fluid injections which help to lubricate the joint and act as a shock absorber for joint loads.

What happens to people with ankle osteoarthritis who get injections with hyaluronic acid compared to placebo after 6 months?

Pain and Physical function were measured using a combined score (scale of 0 to 100; 0 is the best score and 100 the worst)

- People who got injections with hyaluronic acid rated their pain and physical function 12.5 points lower compared to placebo (12% absolute improvement).
• People who got injections with hyaluronic acid rated their pain and physical function 24.4 points lower.
• People who got injections with placebo rated their pain and physical function 12.1 points lower.

Radiographic joint structure changes:
• No studies were found that looked at this outcome.

Quality of life
• No data is available to make a statement about quality of life.
• Number of patients experiencing any serious adverse events:
• No patient in either group experienced a serious adverse event.

Number of patients experiencing any adverse event:
• 35 more people per 1000 who are treated with hyaluronic acid will experience an adverse event compared to placebo (3.5% absolute increase).
• 78 people per 1000 who are treated with hyaluronic acid will experience an adverse event.
• 43 people per 1000 who are treated with placebo will experience an adverse event.

Patient who withdrew because of an adverse event:
• No patients withdrew in either group.
Conservative treatment for osteoarthritis of the ankle

Introduction

Osteoarthritis (OA) is a chronic and degenerative disorder associated with joint pain and loss of joint function. OA can affect any synovial joint but is found most frequently in the hip, knee and hand, the majority of these patients present with primary OA (idiopathic disease) (Buckwalter 2004; Kalunian 2012; Witteveen 2008). Reliable figures on the prevalence of OA in other joints are not readily available but estimates suggest that the incidence of symptomatic ankle OA is 1% to 4% in the adult population (Cushnaghan 1991; Peyron 1984). In contrast to knee and hip OA, 70% to 78% of patients with ankle OA present themselves with secondary, post-traumatic disease, the remainder is primary OA as well as inflammatory diseases, such as rheumatoid arthritis and gout (Saltzman 2005; Valderrabano 2009). Ankle trauma occurs in many patients at a relatively young age (Agel 2005; Saltzman 2005). Consequently, the expected life span of many patients with ankle OA is significantly longer than the life span of hip or knee OA patients; this affects their quality of life for a substantial amount, Saltzman 2006 demonstrated that the self reported physical function in patients with symptomatic ankle OA quantified using the Short Form-36 (SF-36) questionnaire was equivalent to or worse than that of patients with end-stage kidney disease or congestive heart failure suggesting that these patients are seriously impaired.

In clinical practice, patients diagnosed with end-stage OA (Kellgren Lawrence 3 or 4 and van Dijk 3) are offered operative treatment if they have significant clinical symptoms (Harada 2011; van Dijk 1997). These patients are treated by arthrodesis, ankle replacement or osteotomy. Surgical treatment is specifically reserved for end-stage arthritis. It is considered to be harmful due to short and long term complications. Complications consist of wound healing problems, infectious disease, non or delayed union and OA of adjacent joints due to overloading (Chang 2013; Deorio 2008; Jung 2007; Krause 2012; Rippstein 2012; Suckel 2012). Operative treatment is therefore not considered in an early phase of OA, it remains a challenge to treat patients that are diagnosed with a low grade OA of the ankle (Kellgren Lawrence 1, 2 or 3 and Van Dijk 1 or 2) (Harada 2011; van Dijk 1997). They are young and they experience serious disabilities which prevent these patients from participating in more heavily laboured work as well as sports activities.
The conservative treatment of ankle osteoarthritis

Several conservative treatment options are available, however evidence of the benefits and harms of these options are lacking.

The conservative treatment of symptomatic ankle OA, like general OA, consists mainly of treating symptoms like pain and stiffness. Since no cure is available at this point another treatment goal is preventing deterioration of the joint (Towheed 2006). Non-pharmacological therapy is to be considered the foundation for the successful medical management of general OA (Hochberg 2012; Zhang 2008; Zhang 2010). There are systematic reviews published for knee and hip OA and include weight reduction (BMI > 25), physiotherapy and occupational therapy (Brosseau 2011; Brouwer 2005; Rutjes 2009; Rutjes 2010). For ankle OA offloading the joint by brace, cane, rocker sole or inlay can reduce the pain as well (Bartels 2007; Brosseau 2003; Fransen 2009; Janisse 1998; Kempson 1991; Messier 2005; McGuire 2003; Wu 2004). If this is not successful a painkiller can be added. In case of pain relief several options are available, e.g. painkillers like acetaminophen, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) (Cepeda 2006; Garner 2005; Nuesch 2010; Towheed 2006). Hyaluronic acid has been shown to reduce pain as well (Chang 2013; Cohen 2008; Pleimann 2002; Salk 2006; Sun 2006; Witteveen 2008; Witteveen 2010). The benefit of glucosamine/chondroitin for pain reduction in general OA was not shown (Towheed 2005).

Ankle OA pain can be reduced by off loading the joint through rest, wearing a brace or using a cane. A cane can reduce the amount of bodyweight going through the ankle joint by 25% (Kempson 1991). Rockersoles are thought to off load the ankle joint by decreasing the ankle motion at heel strike to push off during walking (Wu 2004). Weight loss by dietary adjustments or exercises are thought to off load a joint as well (Bartels 2007; Brosseau 2003; Fransen 2009). In Messier 2005, each pound of weight loss created a 4-fold reduction in the load exerted by step at the knee during daily activities. Shoe adjustment like inlays can correct alignment issues and in this way off load a part of the joint thus creating pain reduction (Janisse 1998; McGuire 2003). It is possible that in this way the joint can be preserved from further deteriorating. Several analgesics are available like acetaminophen, opioids and NSAIDs. They either act as a simple analgesic, have anti inflammatory effects, a sedative effect or a combination. Recommendations
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for hip, knee or hand OA are well described (Hochberg 2012). Hyaluronic acid (visco supplementation) is thought to restore rheologic properties of the joint by creating a more viscoelastic synovial fluid, which improves mobility and restores the natural protective function of the joint, like shock absorption during gait (Balazs 1993; Bellamy 2006). Several studies have shown pain reduction as well (Chang 2013; Cohen 2008; Pleimann 2002; Salk 2006; Sun 2006; Witteveen 2008; Witteveen 2010). Glucosamine/chondroitine may be potentially chondro protective and may modify the progression and course of general OA. However, up until now no evidence has been found to prove this theory (Towheed 2005).

Lots of treatment modalities are offered, however no clear cut treatment algorithm for ankle OA is used. The choice of treatment depends on the severity of the disease, the patients’ age, medical and social history and the level of physical activity expected to be demanded of the joint. For knee and hip OA several treatment algorithms are advocated (Kalunian 2012; Pendleton 2000; Tannenbaum 2000; Towheed 2005; Towheed 2006; Zhang 2008; Zhang 2010). However, since ankle OA may be caused by a different mechanism, it is not unthinkable that these patients need a different treatment.

At this point there is no evidence based treatment algorithm for ankle OA. Several papers have been published concerning the cause of ankle OA and the possible conservative and operative treatment strategies. The conservative section mainly sums up the possibilities, however no algorithm is suggested (Demetriades 1998; Katcherian 1998; Martin 2007; Rao 2010; Rhys 2003). This review will be conducted to find evidence for the benefits and harms of non-pharmacological and pharmacological treatment of ankle OA in general or by stage of the disease. We will try to provide a synthesis of the evidence as a base for future treatment guidelines.

**Objective**

To assess the benefits and harms of any conservative treatment for ankle OA in adults in order to provide a synthesis of the evidence as a base for future treatment guidelines.
Methods

Criteria for considering studies for this review

Types of studies: All randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were included in this review.

Types of participants: Adults with the diagnosis of symptomatic ankle OA (primary or secondary) were included in this review. The diagnosis was based on well described clinical criteria e.g. the American College of Rheumatology (ACR) criteria (Hochberg 2012), or based on a previously taken X-ray, which was classified using either the Kellgren Lawrence or the Van Dijk scale (Harada 2011; van Dijk 1997).

Types of interventions: Trials investigating any non-surgical intervention were eligible. Trials investigating the following interventions were included:

- pharmacologic therapy: analgesics; acetaminophen, opioid analgesics like codeine, oxycodone or tramadol, NSAIDs like ibuprofen or celecoxib, intra-articular glucocorticoids, intra-articular hyaluronan, glucosamine and chondroitin;
- non-pharmacologic therapy such as weight loss, rest, physical therapy and orthoses: braces, taping, insoles, exercise (strengthening, mobility, endurance and joint stability), manual therapy, diet, self management, psychosocial interventions (Kalunian 2012).

Other methods including traditional medicine (e.g. herbs, acupuncture) and naturopathies were excluded.

We tried to identify two special types of RCTs or CCTs:

- RCTs or CCTs that compared a treatment/therapy alone to placebo; and
- RCTs or CCTs that compared one treatment to the other.

Types of outcome measures

Benefits

- Pain with a hierarchy of seven levels:
  - pain of the affected joint;
  - pain on walking;
- pain on activities other than walking;
- rest pain or pain during the night;
- other algofunctional scale;
- patient’s global assessment;
- physician’s global assessment.

When more than one was reported, the highest on the list was taken.

- Physical function with a hierarchy of eight levels:
  - global disability score;
  - walking disability;
  - disability other than walking;
  - American Orthopedic Foot and Ankle Society score (AOFAS score, Kitaoka 1994);
  - Foot and Ankle Outcome Score (FAOS, Roos 2001);
  - Foot Function Index (FFI, Budiman 1991);
  - Function (Range of Motion (ROM));
  - other algofunctional scale.

When more than one was reported the highest on the list was taken.

- Radiographic joint structure changes according to the given hierarchy:
  - Kellgren Lawrence score (Harada 2011);
  - van Dijk score (van Dijk 1997).

- Quality of Life:
  - Short Form-36 (SF-36, Ware 1992)
  - EuroQoL-5 Dimensions (EQ-5D, Salen 1994).

Harms
- Patients experiencing any serious adverse events (SAEs); a serious adverse event is defined as any adverse event, irrespective of a possible relationship to the administered treatment which leads to e.g. death, a life threatening event or requires hospitalisation.
- Number of patients experiencing any adverse event (AE); an adverse event is
any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.

- Patients who withdraw because of an adverse event or any other reason

If pain or function outcomes were reported at several time-points, the end of treatment was taken as primary time-point for pharmacologic treatment such as acetaminophen, opioids or NSAIDs, with the three months interval as an additional time-point.

In case of hyaluronan, glucocorticoids, glucosamine and chondroitine and nonpharmacologic therapy, six months was considered as primary time-point and the three months interval as an additional time-point.

Search methods for identification of studies

_Electronic searches_: A sensitive search strategy was designed to retrieve trials from electronic bibliographic databases, not limited to any intervention. The search strategy was devised for the OVID Medline interface. The sensitivity maximizing filter for retrieving RCTs from MEDLINE and EMBASE was used as recommended in the Cochrane Handbook (Higgins 2011). No language restriction was applied.

September 11-18, 2014, we searched the following electronic databases, unrestricted by date (from database inception) or language:

- MEDLINE (Ovid) 1946 to present (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 9, 2014) (Appendix 2);
- EMBASE (Ovid) 1947 to present (Appendix 3);
- PsycINFO (American Psychological Association) 1806 to present (Appendix 4);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO) 1985 to present (Appendix 5);
- PEDro (Physiotherapy Evidence Database) (All years (Appendix 6);
- AMED (Allied and Alternative Medicine) (Ovid) 1985 to present (Appendix 7).
We searched the following clinical trial registries to identify ongoing trials:

- ClinicalTrials.gov (http://clinicaltrials.gov/);
- Current Controlled Trials (http://www.controlled-trials.com/);
- The Dutch Register (http://www.trialregister.nl/trialreg/index.asp).

We also screened reference lists in retrieved review articles and trials to identify potentially relevant studies.

Data collection and analysis

Selection of studies: Two authors (AW, CH) independently screened records identified from database searches for possible inclusion. Full-text articles were retrieved for further assessment when the initial information appeared to align with the review criteria. Trials not fulfilling the outlined selection criteria were excluded. Reasons for exclusion were documented. A third author (GK) moderated any disagreement.

Data extraction and management: Two authors (AW, GK) completed data extraction of the included studies and recorded this on a data extraction form. Disagreements were resolved by discussion. We collected data on study design characteristics, descriptive characteristics of the participants, interventions, outcome measures, and length of follow-up. Trialists were contacted for clarification when necessary.

The data extraction included the following:

- Generic publication characteristics:
  - type of publication;
  - title;
  - authors;
  - year of publication.
- Research design:
  - randomised controlled study / controlled clinical trial;
  - blinding of outcome assessors;
  - allocation concealment.
- Descriptive characteristics of participants:
  - number of participants;
- age;
- sex;
- duration of ankle OA;
- grade of ankle OA;
- baseline measures;
- diagnoses; inclusion and exclusion criteria;
- if applicable, randomisation outcomes such as numbers allocated to each group at baseline, withdrawals, intention-to-treat numbers, and losses to follow-up.

**Intervention characteristics:**
- non-surgical intervention: analgesics; acetaminophen, opioid analgesics like codeine, oxycodone or tramadol, NSAIDs such as ibuprofen or celecoxib, intra-articular glucocorticoids, intra-articular hyaluronan, glucosamine and chondroitin;
- non-pharmacologic therapy: weight loss, rest, physical therapy and orthoses: braces, taping, insoles, exercise (strengthening, mobility, endurance and joint stability), manual therapy, diet, self management, psychosocial interventions;
- comparative intervention;
- duration of the intervention (duration (weeks/months) and frequency);
- follow-up.

**Outcomes (benefits and harms):**
- pain;
- safety;
- quality of life;
- physical function.

Disagreements in data extraction were resolved via discussion and further scrutiny of the original data.

**Assessment of risk of bias in included studies:**

The Cochrane Collaboration’s tool for assessing risk of bias (Higgins 2011) was used for assessment of risk of bias in the selected studies. Two authors (AW, GK) independently assessed generation of allocation sequence, allocation concealment, blinding, incomplete
outcome data, selective outcome reporting (reporting bias), and other sources of bias (baseline imbalance in factors which are strongly related to outcome measures e.g. grade of ankle OA; Intervention characteristics e.g. dosage of medication, frequency of therapy). Bias was judged as ‘high risk’ of bias, ‘low risk’ of bias, or ‘unclear’ risk of bias. We resolved disagreements by consensus or discussion with a third author (CH).

Measures of treatment effect

Intervention efficacy and safety were assessed by presenting the mean differences (MDs). In case data could be pooled to perform a meta-analysis, standardised mean differences (SMDs) were used when the same outcome was assessed but different scales were used to express this outcome. A 95% confidence intervals (CIs) was used for continuous outcomes; and risk ratios (RRs) and 95% CIs for dichotomous outcomes. A Peto odds ratio was used for rare events.

Unit of analysis issues

The unit of analysis was the participant. If RCTs or CCTs were identified that treated both ankles, and the number of ankles was used as the denominator in the analysis without adjustment for the non-independence between ankles (and thus a potential of unit of analysis errors might occur), we attempted to re-analyse such studies by calculating sample sizes where possible, according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If it was stated in the article that more than 10% of the patients suffered from general OA, the treatment effect of any treatment for ankle OA would be very difficult to interpret therefore these studies were excluded.

Dealing with missing data

Where we could not directly extract data the trialists were contacted, or missing data was imputed by imputing the missing data with replacement values, and treating these as if they were observed (last observation carried forward) (Higgins 2011). If data was imputed, we noted so in the table ‘Characteristics of included studies’.
Assessment of heterogeneity

We tested heterogeneity of the data using the Chi2 with a P value < 0.10 indicating significant heterogeneity. The I2 statistic was assessed to quantify inconsistency across the results (Higgins 2011) \( I^2 = \frac{Q \text{ df} / Q}{1} \times 100\% \); where Q is the Chi2 statistic and df is the degrees of freedom). A value greater than 50% indicated substantial heterogeneity. Beside this procedure, we also performed a visual assessment of forest plots to assess heterogeneity (Higgins 2011).

Assessment of reporting biases

We investigated selective outcome reporting bias by comparing the study outcomes with those routinely presented for similar studies and also by comparing the methods section of trial reports with the results reported.

Data synthesis

We pooled results of comparable groups of trials. Initially the fixed-effect model and 95% CIs was used. A fixed-effect meta-analysis provided a result that may be viewed as a ‘typical intervention effect’ from the studies included in the analysis. A confidence interval for a fixed-effect meta-analysis was calculated, in order to do so the assumption was made that the true effect of intervention (in both magnitude and direction) was the same value in every study (that is, fixed across studies). This assumption implied that the observed differences among study results were due solely to the play of chance, i.e. that there was no statistical heterogeneity (Higgins 2011). The random-effects model was considered, especially where there was unexplained heterogeneity (Higgins 2011). The Cochrane Collaboration’s statistical software, Review Manager 2013, for data synthesis was used.

Subgroup analysis and investigation of heterogeneity

Due to the lack of data a subgroup analysis was not performed. If sufficient data would be present, an analysis between the benefits and harms of conservative treatments for each grade of OA of the Kellgren Lawrence score (grade 1,2,3) or the van Dijk score (grade 1or 2) would be performed.
Sensitivity analysis

Due to the lack of data the review authors only performed a sensitivity analysis to examine the effects of heterogeneity that was found between studies that were pooled for a meta analysis.

Summary of findings table

The main findings of the study are presented in a “Summary of finding” table, which are produced using GRADEpro software (GRADEprofiler 2008). This table provides key information concerning the quality of the evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes. The table includes an overall grading of the evidence related to each of the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as indicated in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011)(study limitation, indirectness, inconsistency, imprecision, publication bias). A “Summary of findings” is made when sufficient data can be pooled (data synthesis). The important outcomes that were included in the “Summary of findings” tables are:

1. pain;
2. physical function;
3. radiographic joint structures changes;
4. quality of life;
5. number of patients experiencing any serious adverse events;
6. number of patients experiencing any adverse event;
7. patients who withdraw because of an adverse event or any other reason.

Results

After performing the first search up to 11 September 2014, 2945 references were retrieved, after de-duplication this resulted in 2257 citations (1126 Medline, 656 EMBASE, 98 Central, the Cochrane Library, 50 CINAHL, 138 PsychINFO, 14 PEDRO, 175 AMED). No additional studies or ongoing studies were found searching the trial registers. After
screening the titles and abstracts of these references 14 full-text articles were selected, after de-duplication 13 remained. Seven were excluded and 6 were included. See the study flowchart for further details (Figure 1).
The six included studies are listed in the characteristics of included studies table. Years of publication ranged from 2006 to 2014.

All studies are blinded Randomised Controlled Trials (RCT’s), three are double blinded RCT’s (Cohen 2008, DeGroot 2012, Salk 2006). These three studies compared the intra articular injection of Hyaluronic acid (HA) to Placebo. Authors of these studies were contacted by email to get the exact results of the scores they used in their Trials. Cohen 2008 and Salk 2006 were not able to provide us with these data. DeGroot 2012 did send his original database. Two compared two different treatments: HA injection compared to exercise therapy (Karatosun 2008) or HA combined with exercise therapy versus injection of Intraarticular botulinum toxin A (Sun 2014). Witteveen 2010 compared the efficacy and safety of four different doses of HA. A total of 240 participants were involved. All patients were clinically diagnosed with ankle osteoarthritis (ankle OA), which was confirmed radiographically. All participants were in general good health. The Kellgren Lawrence score as well as the van Dijk score was used as classification for the radiographic presence of OA (van Dijk 1997, Kellgren 1957). All studies except Karatosun 2008 investigated patients with unilateral ankle pain. The study population sizes at randomisation varied; 17 (Salk 2006), 75 (Sun 2014), 28 (Cohen 2008), 30 (Karatosun 2008), 64 (DeGroot 2012), 26 (Witteveen 2010). Patients were 18 years or older. Sun 2014 included patients between the age of 20-85 years and Cohen 2008 patients that were 50 years or older.

Follow-up in all studies ranged from 3 to 12 months. Either the Ankle Osteoarthritis Scale (AOS, Domsic 1998) or American Orthopedic Foot and Ankle Society score (AOFAS, Kitaoka 1994) or the Visual Analogue Scale (VAS, Ohnhaus 1975) was used as primary outcome measure. Different types of HA, dosage or dosing schedules were used in each trial. Salk 2006 used 5 weekly injections of 1 ml Hyaluron acid (Hyalgan*) compared to saline. Cohen 2008 used 5 weekly injections of 2ml of Hyaluronic acid (Hyalgan*) compared to 5 injections of 2ml of Saline. Sun 2014 used a single injection of 2 ml Hyaluronic acid (Hyalgan*). Karatosun 2008 used 3 weekly injections of 2.5 ml Hyaluron acid (Adant*). DeGroot 2012 used a single 2 ml injection of Hyaluronic acid (Supartz*) compared to saline. Witteveen 2010 investigated four different doses; single injections of 1, 2, 3 ml, and 3 weekly injections of 1 ml (3X1 ml) of Hyaluronic acid (Orthovisc*).
A total of seven studies were excluded because they were not a randomised controlled trial: Sarkin 1974; Witteveen 2008; Mei-Dan 2010; Luciani 2008; Sun 2011; Huang 2006; Sun 2006. See the table of Characteristics of excluded studies.

Risk of bias in included studies (Fig. 2 and 3.)

Allocation (selection bias): Generally most randomised controlled trials 4/6 described their randomisation process adequately (low risk of bias). Cohen 2008 and Salk 2006 mentioned a randomised component however the process was not described so it was unclear which process was used to conceal allocation.

Blinding (performance bias and detection bias): Three studies (Cohen 2008; DeGroot 2012; Salk 2006) were classified as having a low risk for performance bias and detection bias. Karatosun 2008 was classified as unclear for performance bias, it is most likely, since the patient was not blinded, that the patient informed the physical therapist about the treatment he or she got. Detection bias was considered low for this study because this is most likely of no consequence. For Sun 2014 we assessed a high risk for performance bias, since the patient was and could not be blinded so most likely this information went to the therapist, which could influence the outcome, the secondary outcomes that are measured could be biased by this information so detection bias was considered to be high as well.

Incomplete outcome data (attrition bias): All studies but one were classified as low risk for incomplete data. Salk 2006 described three patients that did not complete the study. However an intention-to-treat analysis (ITT) was not described (unclear risk).

Selective reporting (reporting bias): For DeGroot 2012 it was unclear if there was reporting bias, there was a follow-up of only 3 months, a follow-up of 3 months can be in favour for placebo and therefore affect the results.

Other potential sources of bias: Cohen 2008 was classified as an unclear risk because there was a difference in patient demographics, a significant difference between the mean age of patients in each group was noted as well as a difference between baseline AOS total scores and Western Ontario and McMasters Universities (WOMAC) pain scores Bellamy 1988. DeGroot 2012 was also classified as an unclear risk for other bias since the placebo and treatment group were of unequal sizes, 25 compared to 39. Karatosun 2008 was also classified as having an unclear risk because the group that was assigned to exercise therapy had a significant higher AOFAS score at baseline. Witteveen 2010 was
classified unclear because the study was sponsored by industry, however sponsoring only consisted of supplying hyaluronic acid, the industry was not involved in the development of protocol or manuscript.

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<th>Figure 2: Risk of bias summary: review authors’ judgements about risk of bias item for each included study.</th>
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<td><strong>Cohen 2008</strong></td>
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<td><strong>DeGroot 2012</strong></td>
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<tr>
<td><strong>Karatosun 2008</strong></td>
</tr>
<tr>
<td><strong>Salk 2006</strong></td>
</tr>
<tr>
<td><strong>Sun 2014</strong></td>
</tr>
<tr>
<td><strong>Witteveen 2010</strong></td>
</tr>
</tbody>
</table>
Effects of interventions

Intra articular injection of hyaluronic acid compared to Placebo:


Benefits:

Pain Analysis 1.1

For the outcome pain the AOS pain and/or the total AOS score was used to compare the studies.

In the meta analysis (two studies Cohen 2008 and Salk 2006 ;45 patients) compared to control at 6 months the AOS total score was 12.53 points lower mean difference (MD) in favour for HA. (95% confidence interval (CI) -23.84 to -1.22; Analysis 1.1). We downgraded the quality of evidence from high to low due to the limitation in study design and imprecision of result (low amount of patients). At 3 months (two studies Cohen...
Conservative treatment for osteoarthritis of the ankle

2008, DeGroot 2012; 92 patients) compared to control the total AOS score was 2.26 lower points lower (MD) (95% CI -11.23 to 6.72 Analysis 1.2) We downgraded the quality of evidence from high to low due to inconsistency in the direction and magnitude of the effects across the studies ( I square 89%) and limitation in study design. At 3 months (two studies Cohen 2008, DeGroot 2012; 92 patients) compared to control the AOS sub score pain was1.83 points lower (MD)(95% CI -11.33 to 7.68; Analysis 1.3).

**Physical function** Analysis 1.4

To compare physical function in between studies, the AOS disability score and/or the AOS total score was used.

In the meta analysis at 6 months (two studies Cohen 2008 and Salk 2006; 45 patients) compared to control the AOS total score was 12.53 points lower (MD ) in favour of HA (95% CI -23.84 to -1.22 ; Analysis 1.4).We downgraded the quality of evidence from high to low due to the limitation in study design and imprecision of result( low amount of patients). At 3 months (two studies Cohen 2008, DeGroot 2012; 92 patients) compared to control the total AOS score was 2.26 points lower (MD) (95% CI -11.23 to 6.72; Analysis 1.5). We downgraded the quality of evidence from high to low due to inconsistency in the direction and magnitude of the effects across the studies ( I square 89%) and limitation in study design. At 3 months (two studies Cohen 2008, DeGroot 2012; 92 patients) compared to control the AOS sub score disability was 0.13 points lower (MD) (95% CI -9.26 to 9.01; Analysis 1.6 ).

**Radiographic joint structure** changes were not examined in either study.

**Quality of life** as outcome was only described in two studies Cohen 2008 and Salk 2006 both used the Short-Form 12 (SF12), (Ware 1996).

Cohen 2008: SF12 demonstrated no significant difference in their paper between either group at 6 months, no exact scores were mentioned in the study results and could not be provided upon contacting the author.

Salk 2006: SF12 demonstrated a significant difference in their paper favouring hyaluronic acid at 6 months, No standard deviations were present in the result section of the study, upon contacting the author they could not be provided.
Since the exact scores were not available, no meta analysis could be performed for this score.

**Harms:**

*Analysis 1.7 & Analysis 1.8 & Analysis 1.9*

A meta analysis (three studies Cohen 2008, DeGroot 2012, Salk 2006; 109 patients) showed a similar amount of AEs in either group (Peto Odds ratio (Peto OR) 2.34, 95% CI 0.45 to 12.11; Analysis 1.8). No SAEs were found and no patient withdrew due to an AE; Analysis 1.7, Analysis 1.9)

**Heterogeneity and sensitivity analysis:**

A substantial heterogeneity of 89% was found for Analysis 1.2 and Analysis 1.5. For Analysis 1.3 84% and 89% for Analysis 1.6.

A sensitivity analysis taking each study out of the meta analysis showed a similar result for the Pain Analysis 1.2 and Physical function Analysis 1.5. Due to the low number of eligible studies no further sensitivity analyses were done.

**Intra-articular injection of hyaluronic acid compared to exercise therapy:**

Karatosun 2008 described the comparison of injection HA to exercise therapy (Appendix 8).

**Benefits:**

*Pain* during activity (VAS 0-10) showed a decrease in pain (end point was at 12 months) (MD -0.70; 95% CI -2.54 to 1.14; Analysis 2.1). We downgraded the quality of evidence from high to low due to the unclear risk of bias and small sample size.

*Physical function:* At 12 months compared to exercise the AOFAS score was 13.10 points higher (MD) in favour of hyaluronic acid (95% CI 2.97 to 23.23) on a scale of 0 to 100. We downgraded the quality of evidence from high to low due to the unclear risk of bias (limitation in study design) and small sample size (imprecision of result). At 12 months compared to exercise the walking distance was 0.30 points (MD) better in favour of exercise therapy at 12 months (95% CI -1.27 to 0.67; Analysis 2.2) We downgraded the quality of evidence from high to low due to the unclear risk of bias and small sample size.
Radiographic joint structure changes were not measured.

No quality of life score was measured.

Harms:
No AE’s were found for either group.

Intra-articular injection of hyaluronic acid combined with exercise therapy compared to intra-articular Botulinum toxin A (BoNT-A) injection:
Sun 2014 described the comparison of HA injection combined with exercise therapy to an intra-articular injection of Botulinum toxin A (Appendix 9).

Benefits:

Pain: At 6 months compared to botulinum toxin A the AOS pain score of the affected joint showed a decrease in pain (MD 0.10; 95% CI -0.42 to 0.62: Analysis 3.1). We downgraded the quality of evidence from high to low due to the high risk of bias and small sample size.

Physical function: At 6 months compared to botulinum toxin A the AOS disability score showed a decrease in physical function (MD 0.20; 95% CI -0.34 to 0.74; Analysis 3.2). We downgraded the quality of evidence from high to low due to the high risk of bias and small sample size.

Radiographic joint structure changes were not measured.

No quality of life score was measured.

Harms:
In the HA group 2/37 (5.9%) AE’s were found, in the BoNT-A 2/38 (5.8%) (RR 1.03; 95% CI 0.15 to 6.91; Analysis 3.3). The AE’s consisted of transient injection site reaction and were mild/moderately painful and resolved without treatment.
Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: Effects, safety and dose dependency:

Witteveen 2010 Randomised trial; Four different dosages of intra-articular injections of HA were randomly allocated; 1 ml, 2 ml, 3 ml and 3 weekly injections of 1 ml were compared for efficacy. Primary endpoint of the study was 15 weeks (Appendix 10).

Benefits:

Pain (during walking (VAS)): None of the VAS-scores for ‘pain during walking activities’ decreased significantly at week 15. Best performed the 3X1 ml dose group (P = 0.075). The VAS-scores of the 1, 2, and 3 ml dose groups separately did not change significantly as compared to baseline scores at both secondary endpoints (week 7 and 27) (0.23 < P < 0.74). At week 7, a statistically significant median decrease of the VAS-score of 29 mm was observed in the 3X1 ml dosage group (P = 0.046). The median change in decrease of pain at 27 weeks was best for 3x1ml (-30), however this was not statistically significant (P = 0.25). We downgraded the quality of evidence from high to moderate due to small sample sizes (imprecision of results).

Physical function: No physical function was measured.

Radiographic joint structure changes: Was not measured.

Quality of life: No quality of life was measured.

Harms:

Adverse events: AE’s happened the most in the 2ml group (57%), other groups had an adverse event rate of 14-17%. The total number of AE’s was 7 out of 26 patients (27%). These AE’s consisted of increased pain and swelling of the ankle joint. They were mild or moderate in severity and resolved within 3 days. One patient experienced severe pain and swelling for a week.

No serious adverse events were reported.
Discussion

The search for this review retrieved six randomised controlled trials (RCT), analysing the use of HA for ankle osteoarthritis (OA), no other RCT concerning any other conservative treatment was identified.

A total of 240 patients diagnosed with ankle OA were included in this review. Three studies concerning the comparison of hyaluronic acid to placebo were pooled. A meta analysis was performed to investigate the benefits and harms; HA showed a lower AOS total score than placebo at 6 months. This difference in score was found to be promising, however it is not known if a mean difference of 12.53 points on a 100 point scale is clinically relevant. No minimal important clinical difference is known for this score. At 3 months a small decrease (1.83 points) was found for the AOS sub score pain in favour of HA. The AOS sub score for disability decreased 0.13 points at 3 months in favour of HA. It is not known if these results are clinically relevant, since no minimal important clinical difference is known for this score. Quality of life was difficult to judge due to the fact that the exact numbers were missing, Salk 2006 demonstrated a difference in favour of HA in his paper, Cohen 2008 found similar results between both groups. There was a small number of adverse events in each group with a little preference for HA, see Summary of findings table 1. The Peto odds ratio of developing an adverse event in the intervention group was 2.34 times higher compared to the control group. This evidence is inconclusive because of a wide CI and a small amount of events. Karatosun 2008 compared HA and exercise therapy, a decrease in pain (VAS 0-10) of 0.7 points was found at 12 months. It is questionable if this small decrease in pain is clinically relevant. For physical function at 12 months the total AOFAS score (0-100) was 13.10 higher in favour of hyaluronic acid, this result is considered promising. Sun 2014 described the comparison of hyaluronic acid injection combined with exercise therapy to an intra-articular injection of Botulinum toxin A. A decrease in pain and physical function were found in both groups. The decrease however is small, for pain it was 0.10 and for physical function 0.20 (on a scale of 0-100). Since the reduction in pain and physical function is so small, it is probably not clinically relevant. The amount of adverse events was comparable in both groups. Witteveen 2010 compared 4 different dosing schedules for intra-articular injections of HA for efficacy and safety (26 patients). The best median decrease in pain on walking VAS (on a scale of
0-100) was shown for 3 x 1ml at 27 weeks with a median decrease of 30. Physical function, radiographic changes and quality of life were not measured. The total number of AE’s was 27%, most of them occurred at the 2 ml group (57%). No patients withdrew due to an AE and no SAE’s were noted.

The objective of this review was to assess the benefits and harms of any conservative treatment of ankle OA. No randomised or clinical controlled trials were identified besides the six aforementioned RCTs. These trials all concerned the use of HA infiltrations for ankle OA. No trial (RCT/CCT or ongoing trials) were identified concerning any other conservative treatment. Three trials were pooled, HA was compared to placebo. Different dosage schedules were used between the studies. Cohen 2008 used 5 weekly injections of 2 ml Hyalgan®, Salk 2006 used 5 weekly injections of 1 ml Hyalgan®, where as DeGroot 2012 used a single injection of 2.5 ml of Supartz®. At this point it is unclear what dosage should be used for each type of hyaluronic acid injections. For instance it was found by Witteveen 2010 that 3 x1ml of Orthovisc® performed best for this type of HA. HA restores the rheologic properties of the joint, and is thought to protect the cartilage by improving the viscoelasticity (Balazs 1993; Bellamy 2006). At this point it is not clear which grade of OA responds best to HA infiltrations, however grade 3 van Dijk or grade 4 Kellgren Lawrence are less likely to respond. The three trials included in the meta analysis all included grade 2, 3 and 4 of Kellgren Lawrence without making a subgroup analysis. HA in these studies is thought to improve pain and function, this is mainly the short term of effect, the long term effect, by improving the rheologic properties, is thought to slow down progression of the osteoarthritis of the joint, however none of these studies investigated this outcome. Karatosun 2008 investigated 3 weekly injections of 2.5 ml Adant® to 6 weeks of exercise therapy, these patients suffered sometimes from bilateral ankle OA and knee pain as well, Sun 2014 compared one injection of 2ml of Hyalgan® combined with 4 weeks of 3 weekly sessions of physical therapy to one injection of Botulinum toxin A., Both injections are assumed to improve pain, why exercise therapy was added to hyaluronic acid remains unclear and seems unnecessary. All these differences between studies, the uncertainty about factors like dosage schedule, the ideal grade of ankle OA for this kind of treatment and the lack of evidence for other types of conservative treatment make it difficult to assess the applicability of evidence, at this point no valid recommendations can be made.
Overall the quality of the evidence showed some serious limitations in study design. The evidence was graded as low. There was a limitation in design and implementation and imprecision of the results, sample sizes were small, leading to heterogeneity in the results of the meta analysis. The risk of bias was judged to be at low risk or unclear for all the categories concerning the 3 studies used in the meta analysis. Cohen 2008 was marked unclear because this study showed no clear randomisation and allocation process and there was a baseline imbalance between both groups for age. DeGroot 2012 was marked unclear for other bias because the study had an unequal size in number patients between treatment and placebo group 39/25. The follow-up of this study was limited to 3 months, it is possible that if the follow-up had been longer the treatment group could have performed better due to the diminishing effect of placebo. Salk 2006 was marked unclear because he had no description of the randomisation and allocation process. All trials had a very low number of patients. All 3 studies included Kellgren Lawrence grade IV patients, severe arthritis is known not to respond well to hyaluronic acid treatment, this was also judged as an unclear bias. Karatosun 2008 had an unclear risk of bias because blinding was unclear for the participant, other bias was marked unclear because some patients had bilateral involvement of ankle OA which make judgement of efficacy difficult. Sun 2014 was judged at high risk due to the lack of blinding of patients and evaluators. This limitation in study design and imprecision of results let to a downgrade of two levels in the SOF table, resulting in a low quality. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. No other reasons for downgrading the evidence were found (indirectness of evidence, unexplained heterogeneity, high probability of publication bias).

To minimise the change of bias during the review process, the review was performed according to the published protocol, due to the fact we did find a low number of eligible studies a sensitive search was added in order to include as much studies as possible and to minimise the chance of publication bias. A sensitive search strategy was designed to retrieve trials from electronic bibliographic databases, not limited to any intervention or language. Our search also included a search for ongoing and recently completed trials. However it is still possible that potentially relevant trials have been missed. In order to get additional data from retrieved trials, trialists were contacted, they were forthcoming,
however no further data could be obtained. A meta analysis was conducted and data were pooled, it is possible that due to missing data, unclear biases in the pooled trials, pooling of small sample sizes and comparing trials that used different dosing schedules, data were compared that are not truly comparable, in this way potential bias might be introduced.

The amount of studies and reviews concerning the use of hyaluronic acid for ankle osteoarthritis is very limited. Most studies are included in this review. Three reviews were identified (Abate 2012, Chang 2013, Migliore 2011). One study (Carpenter 2008) was included in all these reviews and was not eligible in our review, since HA was administered arthroscopically after arthroscopic debridement. Abate 2012 reviewed 4 randomised controlled trials and 5 case series. They concluded that there was no evidence on the efficacy of HA in reducing pain and improving function in ankle OA. Their advice for future research was to look at an adequate dose regimen, a good outcome measure, identify which patients and grade of OA benefit best of hyaluronic acid injections. Chang 2013 included 4 randomised controlled trials, 1 double arm and 4 single arm prospective studies. All studies were pooled based on improvement scores from baseline. A significant pain reduction was found for HA. A not significant difference was found in favour for HA comparing HA to placebo. Migliore 2011 included three randomised trials and four single arm studies. Due to the heterogeneity of studies, data could not be pooled. Every study and the conclusion was described. The overall conclusion was that visco supplementation is useful in ankle OA. Future prospective studies need to use standardized outcomes. The present review was restricted to analysis of data from randomised controlled trials, and only comparable data were pooled. It was found that for the total AOS score at 6 months Hyaluronic acid is superior to placebo (MD -11.24; 95% CI -12.30 to -10.18).

HA as treatment for ankle OA appears to be safe and more effective than placebo at 6 months for pain and disability (total AOS score) based on low quality of evidence. Inconclusive results were found comparing HA to other treatments. It remains unclear which patients (age and grade of ankle OA) benefit the most from HA injections and which dosage schedule should be used. Currently, there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis.
To find evidence for conservative treatment of ankle OA; current treatment possibilities, as described in the background section, should be tested against placebo in well conducted randomised controlled trials. Treatment should be tested for age and grade of osteoarthritis. Dosage schedules for medication should be optimised and tested in RCTs. Validated patient and doctor based outcome parameters should be used. Pain and function improvement could be relevant, these parameters can be measured by outcome measures as described in the method section. Radiographic changes can be important to monitor or to evaluate the radiographic progression of osteoarthritis. Evaluation of evidence from different RCTs in combination with the experience from the different specialists in the field of OA, as well as patient’s experiences can lead to a useful guideline for treatment of ankle OA.

Acknowledgements

We like to thank Elizabeth Ghogomu and Tamara Reader and the editorial team of the Cochrane review group for their contributions.

Contributions of authors
- Angelique GH Witteveen: draft the protocol, develop a search strategy, search for trials, select which trials to include, extract data from trials, enter data into Review Manager 2013, interpret the analysis, draft the final review, update the review.
- Cheriel J Hofstad: draft the protocol, develop a search strategy, search for trials, select which trials to include, carry out the analysis
- Gino MMJ Kerkhoffs: draft the protocol, select which trials to include, interpret the analysis, extract data from trials, draft the final review, update the review.

Declarations of interest
One study is included in this review, in which the main author of this review was involved as the main author Witteveen 2010.
Differences between protocol and review

Due to the fact that we found a low number of eligible studies a sensitive search strategy was designed and added to the electronic searches to retrieve trials studies from electronic bibliographic databases, not limited to any intervention.

In measures of treatment effect: A Peto odds ratio was added to be used for rare events.

Since we found a low number of eligible studies, no funnel plots were made to investigate publication bias.

Due to a low number of eligible studies a sensitivity analysis was only performed for heterogeneity that was found between studies that were pooled. It was not possible to examine the effects of important sources of bias, such as whether allocation was concealed, if blinding had been performed properly and if an intention to treat analysis had been performed due to dropout as was described in the protocol.

In the protocol it was stated that if more than one main comparison was found a separate “Summary of findings” tables for each comparison was provided, however since we already found 4 comparisons the amount of SOF tables will be immense when more studies can be included in a future review, therefore it was decided to make a SOF of when a meta analysis of data could be performed.

The following authors that were listed as contributors in the protocol did not take part in either analysing data or carry out the analysis.

- Alfons den Broeder: carry out the analysis, interpret the analysis
- Inger N. Sierevelt: carry out the analysis
Conservative treatment for osteoarthritis of the ankle

References

Included studies

Cohen 2008

DeGroot 2012

Karatosun 2008

Salk 2006

Sun 2014

Witteveen 2010
Excluded studies

Huang 2006

Luciani 2008

Mei-Dan 2010

Sarkin 1974

Sun 2006

Sun 2011
Witteveen 2008

Other references

Abate 2012

Agel 2005

Balazs 1993

Bartels 2007

Bellamy 1988
Bellamy 2006

Brosseau 2003

Brosseau 2011

Brouwer 2005

Buckwalter 2004

Budiman 1991

Carpenter 2008
Cepeda 2006

Chang 2013

Cushnaghan 1991

Demetriades 1998

Deorio 2008
Deorio JK, Easley ME. Total ankle arthroplasty. Instructional Course Lectures 2008;57:383-413.

Domsic 1998

Fransen 2009

Garner 2005
The conservative treatment of ankle osteoarthritis

**GRADEprofiler 2008**

**Harada 2011**

**Higgins 2011**

**Hochberg 2012**

**Janisse 1998**

**Jung 2007**

**Kalunian 2012**
Katcherian 1998

Kellgren 1957

Kempson 1991

Kitaoka 1994

Krause 2012

Martin 2007

McGuire 2003

Messier 2005
Migliore 2011

Nuesch 2010

Ohnhaus 1975

Pendleton 2000

Peyron 1984

Pleimann 2002
Rao 2010

Review Manager 2013

Rhys 2003

Rippstein 2012

Roos 2001

Rutjes 2009

Rutjes 2010

Salen 1994
Saltzman 2005

Saltzman 2006

Suckel 2012

Tannenbaum 2000

Towheed 2005

Towheed 2006
Valderrabano 2009

van Dijk 1997

Ware 1992

Ware 1996

Wu 2004

Zhang 2008

Zhang 2010
Characteristics of included studies:

Cohen 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial (RCT), blinded, parallel group. 5 weekly injections compared to placebo. Primary outcome AOS (pain on movement and weightbearing) for ITT population at 3 months. Secondary outcome (WOMAC) OA index of pain, Physical function, SF12. Follow up at 2 weeks, 6 weeks, 3 months and 6 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>28 participants aged 50 years of older (30 originally at randomisation); Intention to treat consisted of 15 in Hyalgan group (mean age 56.2 (SD 15.1), 1 female, 14 male) and 13 in placebo group (mean age 43.4 (SD 14.9), 2 female, 11 male) Diagnosed with Ankle Osteoarthritis (OA) based on pain and osteoarthritis on X-ray. Kellgren Lawrence stage 2, 3 and 4 were included.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Hyalgan 2ml intra-articular 5 weekly injections versus Saline 2ml intra-articular 5 weekly injections</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain (AOS, WOMAC), Safety (monitoring adverse effects), Quality of Life (SF12, HRQoL), Physical function (WOMAC, AOS) at 2 weeks, 6 weeks, 3 months and 6 months.</td>
</tr>
<tr>
<td>Notes</td>
<td>After randomisation 2 patients declined an injection in either group Results show same outcome as method section.</td>
</tr>
</tbody>
</table>

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>There is no description how the randomisation was performed</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>No description of allocation concealment.</td>
</tr>
<tr>
<td>Blinding of participants</td>
<td>Low risk</td>
<td>For participants it was unclear how they could not be aware of which treatment they got; there is a huge difference between Hyalgan and Saline, difficulty injecting for instance.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>The treating investigator, giving the injections did not conduct the evaluations</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>None, the results cover the same outcome as described in the method section.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>Adverse effects were not clearly described. However the number was low and there was no preference for either group. So it is considered a low risk.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Mean age is statistically different between treatment groups. Stage 4 of Kellgren Lawrence is a severe grade of Osteoarthritis (OA) and not likely to respond on treatment with Hyaluronic acid, it is unclear if there was any baseline imbalance based on the grade of ankle OA.</td>
</tr>
</tbody>
</table>
**DeGroot 2012**

**Methods**
Randomised controlled trial, double blinded, parallel group trial. Primary outcome: change in baseline of AOFAS score at 6 weeks and 12 weeks. Secondary outcomes: Change from baseline AOS score and VAS at 6 and 12 weeks.

**Participants**
64 participants; Ankle Osteoarthritis of at least Kellgren Lawrence grade 2. 39 in Hyaluronic acid group (mean age 54.1 (SD 14.5,2.3), 15 female, 24 male) and 25 in Saline group (mean age 61.9 (SD 14.1,2.8), 13 female, 12 male) Diagnosed with ankle OA based on an x ray, grade 2, 3 or 4 of Kellgren Lawrence system

**Interventions**
Single injection of Supartz hyaluronic acid 2.5 ml intra-articular versus Saline injection

**Outcomes**
Pain (AOFOS, VAS, AOS), Safety (recording adverse effects), Physical function (AOFAS, VAS)

**Notes**
No dose finding, single injection with supartz. 87.5 % of patients completed the study (56/64)

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**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Simple non-block randomisation,</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Selection was based of a selecting an opaque envelop.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>For participants it was unclear how they could not be aware of which treatment they got; there is a huge difference between Hyalgan and Saline, difficulty injecting for instance. However we feel this is of no consequence to the evaluation.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>The treating investigator, giving the injections did not conduct the evaluations.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No missing data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>AOFAS (not validated) is not a common instrument to report the efficacy of hyaluronic acid compared to literature. Follow up is limited to 3 months, it is more common to use 6 months as either primary outcome or additional endpoint. At 3 months the effect of placebo might be higher, thus creating a more positive outcome for placebo (desired outcome) when comparing hyaluronic acid to placebo.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Treatment and placebo group are of unequal size 39 vs 25</td>
</tr>
</tbody>
</table>
Karatosun 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial, blinded, parallel group of 3 weeks Primary outcome AOFAS score. Follow up 1, 2, 3 weeks and 2, 6 and 12 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>30 participants; 15 in Hyaluronic acid group (mean age 52.1 (SD 11.3), 9 female, 6 male) and 15 in exercise group (mean age 58.1 (SD 12.1), 12 female, 3 male) Kellgren Lawrence III Osteoarthritis (OA) Ankle OA could be bilateral.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Hyaluronic acid intra-articular 2.5mg 3 weekly injections versus 6 weeks of daily exercise therapy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Safety (recording of adverse effects), Pain and Physical function as described in the AOFAS: and separated in subsections: VAS testing motion, activity limitation, walking distance, walking surface, gait abnormality, sagittal motion</td>
</tr>
<tr>
<td>Notes</td>
<td>Not clear if there was a minimum age required to be eligible for the study. Not described in method section 43 ankles and 30 patients, some patients had bilateral involvement</td>
</tr>
</tbody>
</table>

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomisation by drawing lots using a computer program</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Well described process.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>It is very well possible that patient told the therapist of the treatment they got.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>It is possible that patient told the therapist of the treatment they got. It is however probably of no consequence to the outcome measurements, since the evaluator was an objective physical therapist.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Outcome in methods section is clearly described in the result section.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No selective outcome reporting. Outcome is consistent with method section.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The group that was assigned to exercises had a significant higher AOFAS score at baseline. Some patients had bilateral involvement of ankle OA which make judgement of efficacy difficult.</td>
</tr>
</tbody>
</table>
Salk 2006

Methods
Randomised controlled trial, blinded, parallel group. Follow up at week 2, 6, 12 and 26. Primary outcome total AOS score. Secondary outcome: Pain (AOS, WOMAC, PGA, 5-point scale), physical function: (Range of Motion, AOS), Ankle girth, Quality of life. Recording of outcome and adverse events at each clinic visit.

Participants
17 participants (20 originally) 18 years or older, chronic ankle pain for more than 3 months, Baseline Total AOS score of more than 30 and less than 90; 9 in Hyalgan group (mean age 57.8 (SD 14.7), 5 female, 4 male) and 8 in Saline group (mean age 60.0 (SD 13.9), 5 female, 3 male) Kellgren Lawrence score of II, III, or IV. AOS score of > 30 and lower than <90 at baseline.

Interventions
Hyalgan 1ml (1mg/ml) intra-articular 5 weekly injections versus Saline 1ml intra-articular 5 weekly injections

Outcomes
Pain (AOS, WOMAC, PGA, 5-point scale), Safety (amount of serious adverse effects, Rescue Medication Tablet), Quality of Life (EQ5D, SF12), Physical function (Range of Motion, AOS), Ankle girth

Notes
Mean and SD for AOS were only shown in a graph at baseline, 3 months and 6 months follow-up. F-values for 6 months follow-up were provided. We contacted the author, he could not provide us with additional data. The SD at 6 months was obtained from Mean Difference data and F-values for differences in means, according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions Chapter 7 (Section 7.7.3.3) (Higgins 2011).
Adverse effects: pain at the injection site 29% adverse effects

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No description of process</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description of process</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>For participants it was unclear how they could not be aware of which treatment they got; there is a substantial difference between Hyalgan and Saline, difficulty injecting for instance.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>The treating investigator, giving the injections did not conduct the evaluations.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Three patients did not complete the study, Intention to treat analysis was not described. However the author confirmed by email that a ITT was undertaken.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results show same outcomes as described in the method section.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Low number of patients. Inclusion criteria: Kellgren Lawrence of IV was also included, this is not common, severe arthritis is known not to respond well to hyaluronic acid treatment.</td>
</tr>
</tbody>
</table>
The conservative treatment of ankle osteoarthritis

Sun 2014

Methods
Randomised controlled trial, blinded, parallel group. Follow up of 6 months, at baseline, 2 weeks, 1 month, 3 months and 6 months. Primary outcome total AOS.

Participants
75 participants, unilateral ankle pain for at least 6 months; Age between 20 and 85. 37 Hyalgan group (mean age 50.6 (SD 10.3), 14 female, 23 male) and 38 in Botuline group (mean age 49.5 (SD 10.9), 15 female, 23 male) At baseline a AOS score of >30 and less than 90 was mandatory. Ankle Osteoarthritis based on an X ray within 6 months of baseline and equivalent with Kellgren Lawrence grade II.

Interventions
Single injection of 2ml hyalgan intra-articular versus Botuline, combined with 12 session (3 weekly for 4 weeks of physical therapy).

Outcomes
Pain (AOS, AOFAS, VAS, Rescue Medication), Safety (registering amount of adverse events), Physical function (AOS, AOFAS, SLS, Timed up and go Test), analgesic consumption, satisfaction.

Notes
Two totally different injections are compared, where at one group even a physical therapy program has been added! why compare these two treatments, where as it made more sense to compare just the 2 without physical therapy.

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Block randomisation; groups of 4</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Block randomisation: groups of 4</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Injection comparing to injection followed by PT, makes it likely that the patient communicated which treatment he underwent. Impossible to blind patients for the therapy they underwent.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>The Secondary outcomes like SLS might be affected by knowing which therapy the patient underwent.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All data was well described.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results show same outcomes as described in the method section.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Unclear what the effect is of two completely different treatment options where one injection +exercise therapy is compared to another injection.</td>
</tr>
</tbody>
</table>
## Methods
Randomised controlled trial, single blinded parallel group trial. Primary endpoint of the study was at 15 weeks. Follow up at 7, 15 and 27 weeks.

## Participants
26 participants, Patients 18 years or older, ankle osteoarthritis based on a recent X-ray, showing grade II ankle OA (van Dijk score), At baseline patients had to score an AOFAS pain score between 20 and 40; 7 patients in 1ml group (mean age 31 (range 26-84), 4 male, 3 female), 7 in 2ml group (mean age 47 (range 33-63), 3 male, 4 female), 6 in 3ml group (mean age 51 (range 39-71), 5 male, 1 female), 6 in 3x1ml group (mean age 40 (range 21-63), 6 female).

## Interventions
Four different dosages were randomly allocated from the storage at the outpatient clinic and injected in the ankle joint, i.e. 1, 2, 3 ml and 3 weekly injections of 1ml. The injection was placed in the anteromedial portal of the ankle joint.

## Outcomes
Pain during walking activities (measured with a 100mm visual analog scale), Pain at night and during the day while at rest (VAS), General pain (4-points scale), the amount of rescue medication, safety (reports of adverse events (AE's)).

## Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Shuffling envelopes</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Opaque sealed envelopes</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and</td>
<td>Low risk</td>
<td>Blinding of patients was not intended</td>
</tr>
<tr>
<td>personnel (performance bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Observer was not aware of dose, however some of the patients were of course aware of the fact that he was assigned to the 3 weekly injections. However we think the outcome is not affected by this.</td>
</tr>
<tr>
<td>(detection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>There was a High dropout of patients, however an intention to treat analysis was undertaken. 9 out of 26 dropouts (35%).</td>
</tr>
<tr>
<td>(attrition bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Primary and secondary outcomes have been reported in the prespecified way</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study was sponsored by Zimmer, hyaluronic acid was supplied without costs. Zimmer had no involvement in developing the protocol or the manuscript, they only supplied the Hyaluronic acid. Data is owned by the authors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Characteristics of excluded studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang 2006</td>
<td>No RCT or CCT</td>
</tr>
<tr>
<td>Luciani 2008</td>
<td>No RCT or CCT, prospective open study</td>
</tr>
<tr>
<td>Mei-Dan 2010</td>
<td>No RCT or CCT, open prospective study</td>
</tr>
<tr>
<td>Sarkin 1974</td>
<td>Unclear diagnosis, unclear outcome</td>
</tr>
<tr>
<td>Sun 2006</td>
<td>No RCT or CCT</td>
</tr>
<tr>
<td>Sun 2011</td>
<td>No RCT or CCT, single arm study</td>
</tr>
<tr>
<td>Witteveen 2008</td>
<td>Open label study, no RCT or CCT</td>
</tr>
</tbody>
</table>
## Summary of findings table

### 1 Hyaluronic acid for osteoarthritis of the ankle

**Hyaluronic acid for osteoarthritis of the ankle**

**Patient or population:** patients with osteoarthritis of the ankle  
**Settings:** Rehabilitation centre / hospital  
**Intervention:** hyaluronic acid  
**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| AOS total (Pain & Physical function) | The mean pain/physical function ranged across the control groups from 6.8 to 20.9 points lower with a weighted mean of 12.14 lower | The mean pain/physical function in the hyaluronic acid group was 12.53 points lower (23.84 to 1.22 lower) at 6 months. | 45 (2 studies) | ☞ ☞ ☞ Low 1 | A lower score indicates less pain and a better physical function. It is not known of a change of 12 points is clinically relevant.  
|                               |                                         |                          |                              |                                 |                                                                                                                                                                                                          |
|                               |                                         |                          |                              |                                 | NNT is 9 (95% CI 7 to 21)  
| AOS total score. Scale from: 0 to 100 (0 = being no pain/disability, 100 = worst Imaginable pain/disability). Follow-up: 6 months |                                         |                          |                              |                                 | Absolute risk difference is -12.53% (95% CI -23.84 to -1.22), relative percentage change is 20.23% (95% CI 2% to 39%).  

---

*Assumed risk Corresponding risk Placebo Hyaluronic acid*
### AOS Pain

**Scale from:** 0 to 100 (0 = being no pain/disability, 100 = worst imaginable pain/disability).

**Follow-up:** 3 months

The mean pain ranged across the control groups from 5.4 to 16.1 points lower with a weighted mean of **12.43 points lower**.

The mean pain in the Hyaluronic acid groups was **1.83 points lower** (11.33 to 7.68 lower) at 3 months.

The mean change in pain for hyaluronic acid was **10.43 points lower** (16.4 to 4.4 lower).

92 (2 studies) ⊕⊕⊝⊝

Absolute risk difference is -1.8% (95% CI -11.3 to -7.7), relative percentage change is 11% (95% CI -47% to 70%).

It is not known of a change of 1.83 points is clinically relevant.

### AOS Physical Function - Disability other than walking -

**Scale from:** 0 to 100 (0 = being no pain/disability, 100 = worst imaginable pain/disability).

**Follow-up:** 3 months

The mean physical function - disability other than walking - ranged across the control groups from 3.9 to 13.4 lower with a weighted mean of **10.21 points lower**.

The mean physical function - disability other than walking in the hyaluronic acid group was **0.13 lower** (9.26 to 9.01 lower) at 3 months.

The mean change in physical function for hyaluronic acid was **9.37 points lower** (15.9 to 2.8 lower).

92 (2 studies) ⊕⊕⊝⊝

Absolute risk difference is -0.1% (95% CI -9.3 to -9.0), relative percentage change is 1% (95% CI -67% to 70%).

It is not known of a change of 0.13 is clinically relevant.

### Radiographic Joint Structure Changes

See comment

Not estimable (0)

See comment

Radiographic joint structure changes were not investigated.

### Quality of Life SF12. Scale from: 0 to 100.

**Follow-up:** mean 6 months.

See comment

Not estimable

See comment

Cohen only described that there was no significant difference between placebo and intervention for the SF12 outcome, no exact data was provided.

Salk could not provide us with the standard deviations, so no estimate of the SF 12 could be made.
Conservative treatment for osteoarthritis of the ankle

<table>
<thead>
<tr>
<th>Number of patients experiencing any serious adverse events</th>
<th>See comment</th>
<th>See comment</th>
<th>Not estimable</th>
<th>109 (3 studies)</th>
<th>See comment</th>
<th>No serious adverse events (SAEs) were noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: 3-6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Number of patients experiencing any adverse event | 43 per 1000 (18 to 285) | 78 per 1000 (18 to 285) | RR 1.66 (0.47 to 5.88) | 109 (3 studies) | ⊕⊕⊕⊕ low1 | Peto Odds Ratio is 2.34 (95% CI 0.45 to 12.11) |
| Follow-up: 3-6 months                                  |             |             |                      |                |             |                                           |

| Patients who withdrew because of an adverse event or any other reason | See comment | See comment | Not estimable | 109 (3 studies) | See comment | No patients withdrew because of an adverse event |
| Follow-up: 3-6 months                                      |             |             |               |                |             |                                           |

AOS: Ankle Osteoarthritis Scale
CI: Confidence interval;
RR: Risk ratio;
OR: Odds ratio;
SF12: short form 12

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Grade criteria: study limitation, indirectness, inconsistency, imprecision, publication bias.
Footnotes

* The assumed risk was based on the weighted mean of the scores in the control groups across the 2 studies. The range was based on the mean of the control group in each separate study. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

1 Evidence was downgraded based on limitations in study design and imprecision of results. Limitation in study design: there was a unclear risk of selection bias for Salk and Cohen, unclear risk for attrition bias for Salk. Imprecision of results: the population size is small (45 patients). No indirectness of evidence was found, no inconsistency and no publication bias.

2 Evidence was downgraded based on limitations in study design and imprecision of results. Limitation in study design: there was a unclear risk of selection bias for Cohen, an unclear risk for reporting bias for DeGroot. Imprecision of results: the total population size is small (92 patients). No indirectness of evidence was found, no inconsistency and no publication bias.
Data and analyses

1 Hyaluronic acid versus Placebo

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Pain- AOS_total_6months</td>
<td>2</td>
<td>45</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-12.53 [-23.84, -1.22]</td>
</tr>
<tr>
<td>1.2 Pain- AOS_total_3months</td>
<td>2</td>
<td>92</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.26 [-11.23, 6.72]</td>
</tr>
<tr>
<td>1.3 Pain- AOS_pain_3months</td>
<td>2</td>
<td>92</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.83 [-11.33, 7.68]</td>
</tr>
<tr>
<td>1.4 Physical Function- AOS_total_6months</td>
<td>2</td>
<td>45</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-12.53 [-23.84, -1.22]</td>
</tr>
<tr>
<td>1.5 Physical Function- AOS_total_3months</td>
<td>2</td>
<td>92</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.25 [-11.23, 6.72]</td>
</tr>
<tr>
<td>1.6 Physical Function- AOS_disability_3months</td>
<td>2</td>
<td>92</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.13 [-9.26, 9.01]</td>
</tr>
<tr>
<td>1.7 Serious adverse events</td>
<td>3</td>
<td>109</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.8 Any adverse events</td>
<td>3</td>
<td>109</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>2.34 [0.45, 12.11]</td>
</tr>
<tr>
<td>1.9 Patients who withdraw because of an adverse event</td>
<td>3</td>
<td>109</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Analysis 1.1

Analysis 1.2
The conservative treatment of ankle osteoarthritis

**Analysis 1.3**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic acid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Cohen 2008</td>
<td>-20.17</td>
<td>22.27</td>
<td>15</td>
<td>-5.35</td>
</tr>
<tr>
<td><strong>Total (96% CI)</strong></td>
<td></td>
<td></td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 6.22, df = 1 (P = 0.01); I² = 64%
Test for overall effect: Z = 0.38 (P = 0.71)

**Analysis 1.4**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic acid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Saks 2008</td>
<td>-32.1</td>
<td>22.55</td>
<td>9</td>
<td>-20.67</td>
</tr>
<tr>
<td>Cohen 2008</td>
<td>-19.8</td>
<td>19.9</td>
<td>15</td>
<td>-6.77</td>
</tr>
<tr>
<td><strong>Total (98% CI)</strong></td>
<td></td>
<td></td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)

**Analysis 1.5**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic acid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2008</td>
<td>-23</td>
<td>20.61</td>
<td>15</td>
<td>-4.94</td>
</tr>
<tr>
<td><strong>Total (98% CI)</strong></td>
<td></td>
<td></td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 8.66, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.49 (P = 0.62)

**Analysis 1.6**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic acid</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2008</td>
<td>-23.8</td>
<td>24.48</td>
<td>15</td>
<td>-3.91</td>
</tr>
<tr>
<td><strong>Total (96% CI)</strong></td>
<td></td>
<td></td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 8.89, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 0.03 (P = 0.98)
Conservative treatment for osteoarthritis of the ankle

Analysis 1.7

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2008</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>13</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>DeGroot 2012</td>
<td>0</td>
<td>39</td>
<td>0</td>
<td>25</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Salk 2006</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>8</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>46</td>
<td></td>
<td></td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis 1.8

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2008</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>13</td>
<td>6.47 [0.13, 329.19]</td>
<td>Peto, Fixed, 95% CI</td>
</tr>
<tr>
<td>DeGroot 2012</td>
<td>1</td>
<td>39</td>
<td>0</td>
<td>25</td>
<td>5.16 [0.09, 290.65]</td>
<td>Peto, Fixed, 95% CI</td>
</tr>
<tr>
<td>Salk 2006</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>8</td>
<td>1.46 [0.19, 11.08]</td>
<td>Peto, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>46</td>
<td></td>
<td></td>
<td>2.34 [0.48, 12.11]</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total events</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 0.61, df = 2 (P = 0.74); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Z = 1.01 (P = 0.31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
</tbody>
</table>

Analysis 1.9

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 2008</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>13</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>DeGroot 2012</td>
<td>0</td>
<td>39</td>
<td>0</td>
<td>25</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Salk 2006</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>8</td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>46</td>
<td></td>
<td></td>
<td>Not estimable</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 2 Hyaluronic acid versus Exercise therapy

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Pain during activity- VAS (AOFAS)</td>
<td>1</td>
<td>30</td>
<td>Mean Difference (IV, Fixed, 95% CI [AOFAS])</td>
<td>-0.70 [-2.54, 1.14]</td>
</tr>
<tr>
<td>2.2 Walking distance (AOFAS) [AOFAS]</td>
<td>1</td>
<td>30</td>
<td>Mean Difference (IV, Fixed, 95% CI [AOFAS])</td>
<td>-0.30 [-1.27, 0.67]</td>
</tr>
<tr>
<td>2.3 Physical Function, total AOFAS [AOFAS-total]</td>
<td>1</td>
<td>30</td>
<td>Mean Difference (IV, Fixed, 95% CI [AOFAS-total])</td>
<td>13.10 [2.97, 23.23]</td>
</tr>
<tr>
<td>2.4 Adverse Event</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

### Analysis 2.1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Progressive Ankle Exercises</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Mean AOFAS</td>
<td>-3.1 (SD 1.9)</td>
<td>3.1 (SD 1.3)</td>
<td>-0.70 [-2.54, 1.14]</td>
<td>-0.70 [-2.54, 1.14]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 0.75 (P &gt; 0.48)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 2.2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Progressive Ankle Exercises</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Mean AOFAS</td>
<td>1.4 (SD 1.4)</td>
<td>1.7 (SD 1.3)</td>
<td>-0.30 [-1.27, 0.67]</td>
<td>-0.30 [-1.27, 0.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 0.81 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Analysis 2.3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Progressive Ankle Exercises</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Mean AOFAS-total</td>
<td>26.5 (SD 9.7)</td>
<td>15.4 (SD 17.5)</td>
<td>13.10 [2.87, 23.23]</td>
<td>13.10 [2.87, 23.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 2.54 (P &lt; 0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 2.4

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Progressive Ankle Exercise</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Mean</td>
<td>0</td>
<td>15</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 3 Hyaluronic acid versus Botulinum toxin A

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Pain_AOS-pain</td>
<td>1</td>
<td>75</td>
<td>Mean Difference (IV, Fixed, 95% CI [AOS_pain])</td>
<td>0.10 [-0.42, 0.62]</td>
</tr>
<tr>
<td>3.2 Physical Function_AOS-disability</td>
<td>1</td>
<td>75</td>
<td>Mean Difference (IV, Fixed, 95% CI [AOS_disability])</td>
<td>0.20 [-0.34, 0.74]</td>
</tr>
<tr>
<td>3.3 Adverse events</td>
<td>1</td>
<td>75</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.03 [0.15, 6.91]</td>
</tr>
</tbody>
</table>

#### Analysis 3.1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Botulinum</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun 2014</td>
<td>-2</td>
<td>1.1</td>
<td>37</td>
<td>-2.1</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

#### Analysis 3.2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Botulinum</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [AOS_disability]</td>
<td>SD [AOS_disability]</td>
<td>Total</td>
<td>Mean [AOS_disability]</td>
</tr>
<tr>
<td>Sun 2014</td>
<td>-2.1</td>
<td>1.1</td>
<td>37</td>
<td>-2.3</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

#### Analysis 3.3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyaluronic Acid</th>
<th>Botulinum</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Sun 2014</td>
<td>2</td>
<td>37</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>38</td>
<td>100.0%</td>
<td>0.00</td>
</tr>
<tr>
<td>Total events</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 0.03 (P = 0.99)
Appendices

MEDLINE search strategy

Search terms for design
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9

Search terms for population
11. Ankle/ or Ankle Joint/
12. ankle.af.
13. exp Osteoarthritis/
14. exp Arthritis/
15. (osteoarthritis or arthritis or arthrosis or osteoarthrosis or (degenerative adj (arthr$ or disease))).af.
16. 11 or 12
17. 13 or 14 or 15
18. 16 and 17

Combining terms
19. 10 and 18
2 CENTRAL search strategy

1. MeSH descriptor Osteoarthritis explode all trees
2. MeSH descriptor arthritis explode all trees
3. (osteoarthritis OR arthritis OR arthrosis OR osteoarthrosis OR (degenerative near/3 (arthr* OR disease)))
4. MESH descriptor ankle
5. MESH descriptor ankle joint
6. #4 OR #5
7. ankle
8. (#1 OR #2 OR #3)
9. (#6 OR #7)
10. (#8 AND #9)

3 EMBASE search strategy

Search terms for design
1. randomised controlled trial.sh.
2. randomization.sh.
3. exp clinical trials/
4. (clin$ adj25 trial$).ti.ab
5. random$.ti.ab.
6. or/1-4

Search terms for population
6. 6 Ankle/ or Ankle Joint/
7. 7 ankle.af.
8. 8 exp Osteoarthritis/
9. 9 exp Arthritis/
10. 10 (osteoarthritis or arthritis or arthrosis or osteoarthrosis or (degenerative adj3 (arthr$ or disease))).ti.ab.
11. 6 or 7
12. 8 or 9 or 10
13. 11 and 12

Combining terms
14. 5 and 13

4 PsycINFO search strategy

Search terms for design
1. clinical trial.mp or exp Clinical Trials
2. randomised controlled trial.mp.
3. clinical trial*.af.
4. random*.af.
5. placebo.af.
6. (randomised controlled trial or controlled clinical trial).af. or trial .ti.
7. 1 or 2 or 3 or 4 or 5 or 6 or 7
8. limit 7 to human

Search terms for population
9. exp Ankle/
10. ankle.af. or ankle joint.af.
11. 9 or 10
12. exp Arthritis/
13. (osteoarthritis or arthritis or arthrosis or osteoarthrosis or (degenerative ~ (arthr* or disease))).af.
14. 12 or 13 or 14
15. 11 and 15

Combining terms
16. 8 and 15
5 CINAHL search strategy

Search terms for design
1. (MH “Clinical Trials+”)
2. (MH “Random Assignment”)
3. TX (clin$ n25 trial$)
4. TX random$
5. S1 or S2 or S3 or S4

Search terms for population
6. Osteoarthritis
7. (MH “Osteoarthritis”)
8. TX osteoarthritis
9. TX arthritis
10. TX osteoarthrosis
11. TX degenerative n3 disease
12. Ankle
13. Ankle joint
14. TX ankle
15. S6 or S7 or S8 or S9 or S10 or S11
16. S12 or S13 or S14
17. S15 and S16

Combining terms
18. S5 and S17

6 PEDro search strategy

1. Osteoarthritis in title or abstract
2. Method: clinical trial
3. Body part: foot or ankle
Combination 1 and 2 and 3
7 AMED search strategy

1. Ankle/ or Ankle Joint/
2. ankle.af.
3. exp Osteoarthritis/
4. exp Arthritis/
5. (osteoarthritis or arthritis or arthrosis or osteoarthrosis or (degenerative adj (arthr$ or disease))).af.
6. 1 or 2
7. or/3-5
8. or/3-5
9. 6 and 7
10. exp Surgery/
11. Surgery operative/
12. surg$.tw.
13. surg$.tw.
14. 10 or 11 or 12
15. 11 or 12 or 13
16. 9 not 14

8 Results included studies: Karatuson 2008

<table>
<thead>
<tr>
<th></th>
<th>follow-up 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAIN</td>
</tr>
<tr>
<td></td>
<td>Pain during activity - VAS SD (mean)</td>
</tr>
<tr>
<td>Hyaluronic acid (HA) group</td>
<td>n=15</td>
</tr>
<tr>
<td>Progressive Ankle Exercise</td>
<td>n=15</td>
</tr>
</tbody>
</table>

Karatuson 2008
9 Results included studies: Sun 2014

Sun 2014

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosage</th>
<th>Follow-up</th>
<th>AOS-pain SD (mean)</th>
<th>Pain VAS SD (mean)</th>
<th>AOS-disability SD (mean)</th>
<th>AOFAS SD (mean)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronate</td>
<td>n=37</td>
<td>6 months</td>
<td>from 4.5 (1,1) to 2.5 (1,1)</td>
<td>from 3.9 (1,2) to 1.7 (1,1)</td>
<td>from 5.0 (1,3) to 2.9 (1,1)</td>
<td>from 70.0 (11,7) to 86.4 (12,5)</td>
<td>2 patients (5.9%) reported mild to moderate pain</td>
</tr>
<tr>
<td>Botulin</td>
<td>n=38</td>
<td>reconstituted in 2cc normal saline</td>
<td>from 4.5 (1,3) to 2.4 (1,2)</td>
<td>from 4.0 (1,8) to 1.8 (0,9)</td>
<td>from 5.2 (1,9) to 2.9 (1,3)</td>
<td>from 17.3 (11,6) to 88.3 (7,2)</td>
<td>2 patients (5.6%) reported mild to moderate pain</td>
</tr>
</tbody>
</table>

10 Results included studies: Witteveen 2010

<table>
<thead>
<tr>
<th>Dosage Group</th>
<th>VAS Pain Median (Range)</th>
<th>VAS Pain Median Change (Range)</th>
<th>VAS Pain Median Change (Range)</th>
<th>General Pain (% Improvement at 27 weeks)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ml n=7</td>
<td>43 (7 to 71)</td>
<td>-7 (-35 to 21)</td>
<td>1 (-58 to 22)</td>
<td>6 (-22 to 22)</td>
<td>0% 14% (1 patient reported mild to moderate pain)</td>
</tr>
<tr>
<td>2ml n=7</td>
<td>81 (46 to 100)</td>
<td>-9 (-65 to 13)</td>
<td>-7 (-97 to 19)</td>
<td>-7 (-71 to 19)</td>
<td>0% 57% (4 patients reported mild to moderate pain)</td>
</tr>
<tr>
<td>3ml n=6</td>
<td>48 (24 to 87)</td>
<td>-6 (-39 to 10)</td>
<td>-7 (-41 to 2)</td>
<td>-7 (-87 to 17)</td>
<td>0% 17% (1 patient reported mild to moderate pain)</td>
</tr>
<tr>
<td>3x1ml n=6</td>
<td>61 (16 to 88)</td>
<td>-29 (-78 to 7)</td>
<td>-47 (-78 to 26)</td>
<td>-30 (-78 to 26)</td>
<td>67% 17% (1 patient experienced severe pain)</td>
</tr>
</tbody>
</table>