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The conservative treatment of ankle osteoarthritis
Witteveen, A.G.H.

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Summary: The conservative treatment of ankle osteoarthritis
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Chapter 1: General 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.

Reliable figures on the prevalence of OA in the ankle are not readily available but estimates suggest that the incidence of symptomatic ankle OA is 1% to 4% in the adult population.

Many treatment modalities are offered. The conservative treatment of symptomatic ankle OA consists mainly of treating symptoms like pain and stiffness. 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 to be demanded of the joint.

Although sufficiently evaluated for application in the knee, evidence for efficacy, safety and dosing of hyaluronic acid in the ankle is limited. A complicating issue is the technically demanding injection procedure.

To monitor the effect of conservative treatment modalities for ankle OA it is important to agree on which outcome to use. Outcome measures that are used nowadays are created with little input of the target patient group. In this respect, it is important to know the impact of ankle OA for patients on daily life in order to measure the effect of treatment.

At this point evidence for the use of conservative treatment for ankle OA is limited. It is unclear which treatments are used before patients are referred to the hospital and at what stage patient are referred to the hospital.

This thesis addresses the efficacy and safety of hyaluronic acid injections for ankle OA, the dosage schedule of HA and the optimum injection technique for the osteoarthritic ankle. Additionally, the impact of ankle OA on daily life and the available evidence for conservative treatments of ankle OA are evaluated. Finally, the stage of ankle OA at which patients are referred to a tertiary center, what treatment they underwent, the cause of their ankle OA and the treatment that was prescribed are addressed.
Chapter 2: A prospective multicenter, open study of the safety and efficacy of hylan G-F 20, in patients with symptomatic ankle osteoarthritis

The purpose of the study was to evaluate the safety and efficacy of hylan G-F 20 (Synvisc) in patients with ankle osteoarthritis.

A prospective, open study was performed in patients with symptomatic ankle osteoarthritis.

Patients received a single injection in the ankle joint of 2 ml of Hylan G-F 20 plus an optional second injection after 1, 2 or 3 months. Patients with symptomatic ankle OA, evidenced by a score between 50 mm and 90 mm on the ankle OA pain scale of 0-100 mm, were eligible. The primary efficacy endpoint was the change from baseline in the pain VAS score at 3 months. The safety assessment was based on reports of adverse events (AEs), during follow up.

Fifty-five patients received the first injection; 24 received a second injection. There were no serious or severe adverse events related to the treatment. Seventeen patients experienced mild or moderate local, treatment related AEs. The mean pain VAS score decreased from 68.0 at baseline to 33.8 at 3 months (p<0.001), which was maintained to 6 months (34.2 mm, p<0.001).

The conclusion is that Hylan G-F 20 is well-tolerated and effective for up to 6 months in the treatment of symptomatic ankle osteoarthritis.

Chapter 3: The efficacy, safety and dose dependency of intra-articular hyaluronic acid (HA) injections in the osteo-arthritic ankle joint

The ideal dose and frequency of HA injections in the ankle is not determined yet.

The aim of the study was to determine the efficacy, safety and dose dependency of intra-articular HA injections in the osteo-arthritic ankle joint.

A prospective single blinded study in patients with symptomatic ankle OA was carried out. Patients were allocated to 1, 2, 3 ml or 3 weekly injections of 1 ml (3x1ml). The primary outcome was ‘pain during walking’ at 15 weeks measured on a 100 mm VAS.

Twenty-six patients participated. The 3 x 1 ml dose group showed statistically significant decreases at week 7 for ‘pain during walking’ and ‘pain at rest’ (p=0.046). At week 15 decreases were significant for ‘pain at rest’ (p= 0.046). There were no significant
decreases of VAS - scores in any of the single dose groups. Seven patients experienced temporary local swelling and increased pain in the injected ankle.

It was concluded that Orthovisc® viscosupplementation in the ankle joint is effective and well tolerated. The 3x1ml dose regimen showed the best results.

Chapter 4: The optimal injection technique for the osteoarthritic ankle: a randomized crossover trial

In order to optimize the injection technique for the osteoarthritic ankle, in order to enhance the effect of intra-articular injections and minimize adverse events, two injection techniques in patients with symptomatic ankle osteoarthritis were compared using a randomized crossover trial.

The primary aim of this study was to investigate the accuracy of intra-articular injections in the osteo-arthritic ankle joint using the traction device compared to the injection technique that is commonly used for the ankle joint.

Patients received an injection with hyaluronic acid using either one of the techniques. Four weeks later the second injection was given using the other technique. Primary outcome was the failure rate of the injection.

Seventy patients fulfilled the study. The failure rate for both injection techniques was similar (24%). Forty-one patients in the traction group and thirty-nine in the group without traction, experienced treatment related local adverse events. Other secondary outcomes did not show any difference between injection techniques.

Because there was a relevant failure rate in both groups it is concluded that the use of contrast-aided fluoroscopy for injecting the severe osteoarthritic ankle can be advised at all times.

Chapter 5: The impact of ankle osteoarthritis. The difference of opinion between patient and orthopedic surgeon

Different scoring systems are used to monitor the effects of conservative treatment modalities, these outcome scores are created by physicians with little input of the target patient group.
In order to get a patient reported outcome measure (PROM) that monitors clinical outcome in ankle OA patients, it is imperative to know what is considered relevant for the target patient group.

A modified Delphi method was used, consisting of structured interviews with patient focus groups and experts, followed by a poll using 32 statements, which were created using existing outcome scores. The difference in opinion between patients and orthopedic surgeons was evaluated. Forty patients and forty orthopedic surgeons responded to the 32 formulated statements. Pain was considered the most important symptom of ankle OA by patient and orthopedic surgeon. An important item that was mentioned by patients was their difficulty to perform certain activities and their wish to participate in daily life and sport activities. Stiffness is a symptom that hinders patients in performing in daily activities, this was less appreciated by orthopedic surgeons.

A significant difference in opinion between patients and orthopedic surgeons concerning specific symptoms of ankle OA was demonstrated, leading to the conclusion that incorporating the needs and demands of the individual patient for new outcome measures seems a logical next step in creating a new PROM.

Chapter 6: Conservative treatment of ankle osteoarthritis; a Cochrane review

In order to provide a synthesis of the evidence as a base for future treatment guidelines, a review of the available high quality evidence regarding the benefits and harms of conservative treatment for ankle OA in adults was undertaken.

The cause of ankle osteoarthritis (OA) is mainly posttraumatic. 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.

The major databases were searched from their start to September 2014. Randomized or Controlled Clinical trials investigating any non-surgical intervention for ankle osteoarthritis were considered for inclusion.

Six randomized controlled trials (RCT), analyzing the use of hyaluronic acid for ankle osteoarthritis (OA) were retrieved, 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-articular injection of botulinum toxin and one compared four different dosages of HA.

For pain and physical function, a pooled analysis of two trials (45 patients) found that the Ankle Osteoarthritis Scale (AOS) total score was reduced by 12% (95% CI -24% to -1%) in the HA group compared to placebo at six months (mean difference (MD) -12.53 (95% CI -23.84 to -1.22) on a scale of 0 to 100; NNT= 9, this evidence was graded as low, due to imprecision and limitations in study design. The AOS sub score pain was decreased at 3 months (92 patients) (MD -1.83; 95% CI -11.33 to 7.68). The AOS sub score disability (physical function) at 3 months (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. 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 on a Visual Analogue Scale (VAS 0-10) was decreased at 12 months compared (MD-0.70 95% CI -2.54 to 1.14).

For the comparison of HA injection combined with exercise therapy to an intra-articular injection of Botulinum toxin 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 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.

It is concluded that up to date there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis. 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.
Chapter 7: Evidence for conservative treatment of ankle osteoarthritis is lacking: at what stage are patients referred to the orthopedic surgeon?

To monitor conservative treatment for ankle osteoarthritis (ankle OA) for efficacy and safety, to provide evidence for a treatment algorithm, patients need to be referred for treatment in an early stage of the disease.

Between March 2011 and September 2013, data of ankle OA were collected and analyzed. It was investigated at what stage patients were referred to an orthopedic clinic, which conservative treatment was used before referral and what treatment options were possible at referral.

Hundred ninety-seven patients were prospectively included. The majority of patients were referred to us at a relatively late stage of ankle OA; 53% at van Dijk grade 2B and 3, 62% at Kellgren-Lawrence grade 3-4. Prior treatment consisted mainly of the use of an assistive device like an orthopedic shoe/crutch. Pain medication was used the most by grade 3 patients and consisted mainly of NSAIDs. Treatment advice at the end of the clinic visit consisted in case of grade 3 patients mainly of surgical treatment (71%), other possible options were hyaluronic acid injections, assistive devices, physical therapy of a combination of these options.

The conclusion of this study was that patients are referred at a late phase of the disease. If we want to find evidence for different conservative treatment options and to understand the process of ankle OA it is essential that patients are referred at an early phase of ankle OA.

Chapter 8: General discussion and summary

Evidence for conservative treatment is limited. The research described in this thesis was aimed to find evidence for the efficacy and dose regimen of hyaluronic acid (HA) for ankle OA. In order to enhance efficacy of HA and reduce the amount of adverse events, attempts were made to find the optimum injection technique for ankle OA. The impact of ankle OA on daily life comparing the opinion of patients to orthopedic surgeons was investigated. A systematic review of the literature was undertaken to find evidence for existing conservative treatments for ankle OA. In order to explore the current use of conservative therapy for ankle OA, a cohort of ankle OA patients was investigated for the use of conservative treatment before referral to the hospital, for the stage of ankle
OA at which patients were referred and for the treatments that could be offered to them, specifically where it concerned the conservative options.

This thesis demonstrated that a single injection of 2 ml Hylan GF-20 with an optional second injection after 1, 2 or 3 months was effective in significantly reducing the pain associated with ankle OA. Pain reduction was maintained up to six months in the majority of the patients. Four different dosages were compared for the use of Orthovisc, the 3x1 ml regimen showed the best results for pain on walking for this brand.

Two injection techniques were compared; the same failure rate was demonstrated leading to the recommendation that the best way to inject the ankle is with the aid of the fluoroscope until other techniques have proven themselves.

Several significant differences in opinion between patients and orthopedic surgeons were demonstrated. One of the most important differences is the fact that patients have difficulty to perform certain activities. Clinicians with little or no input of the patient target group make proms that are currently used. The results of this study led to the conclusion that if we desire a truly patient reported outcome (PROM), we need, besides the outcome that is important to the clinician, to incorporate the needs and demands of the individual patient.

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 a Cochrane review of the existing literature was performed. It was concluded that up to date there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis. Patients are referred in such a late stage of ankle OA that the only treatment option mainly existed of a surgical solution. Before referral to the hospital different treatment options are used in a random order. In order to find evidence for conservative treatment patients need to be referred in an early stage of the disease.

It is recommended that more high quality studies are needed to find evidence for conservative treatments of early ankle OA. These studies are required to create a future guideline. Due to the higher volume of patients and other available resources it is preferable to perform this research in a hospital setting. For this, patients need to be referred to the hospital in an early stage of the disease. Primary care physicians and other professionals involved in treatment of ankle OA patients have to be aware of the process of the development of ankle OA in order to recognize patients that are at risk.
Future research should also be aimed at the prevention of the development and progression of ankle OA.