The conservative treatment of ankle osteoarthritis
Witteveen, A.G.H.
CHAPTER 3

Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency

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Abstract

Background: To determine the efficacy, safety and dose dependency of intra-articular Orthovisc® hyaluronic acid injections in the ankle.

Methods: A prospective single blinded study in patients with symptomatic ankle – osteoarthritis. Patients were randomly allocated to 1 ml, 2 ml, 3 ml, or 3 weekly injections of 1 ml (3x1 ml). Primary outcome was ‘pain during walking’ at 15 weeks measured on a 100 mm VAS.

Results: Twenty-six patients (ITT) participated. The 3x1 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 was no significant decrease of VAS-scores in any of the single dose groups. Seven patients experienced temporary local swelling and increased pain in the injected ankle.

Conclusions: Orthovisc® viscosupplementation in the ankle joint is effective and well tolerated. The 3x1 ml dose regimen shows the best results.

Keywords: Ankle joint, Osteoarthritis, Hyaluronic acid, Intra-articular injections.
Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency

Introduction

Hyaluronic acid injections are frequently used as a treatment for ankle joint osteoarthritis [1-5]. The ideal dose and injection frequency has not been determined yet. The aim of this current study was to determine efficacy, safety and dose dependency of intra-articular sodium hyaluronate injections (Orthovisc®) in the osteoarthritic ankle.

Materials and Methods

Study design

This study was designed as a longitudinal prospective single blind study; in the respect that the observer was blinded for the type of treatment the patient had received.

At screening visit, 2 weeks before the patients entered the study, the patient’s suitability was assessed and they were informed about the study. Written, informed consent was obtained from each patient prior to enrolment in the study.

After signing the informed consent, patients were randomised to one of the four treatment groups with the use of radio-opaque sealed envelopes. The blinded observer carried out the physical ankle assessment of the patient and had supervision on the patient’s completion of the questionnaires at baseline prior to the (first) injection and at the follow-up evaluations. At baseline (week 0) four dosages were randomly allocated from the storage at the outpatient clinic and injected in the ankle joint i.e. 1 ml, 2 ml, 3ml and 3 weekly injections of 1 ml (3x1 ml). Injections were performed by one of the surgeons (CvD) according to a standardized protocol.

The injection was placed in the anteromedial portal of the ankle joint as described for ankle arthroscopy [6]. Before the HA injection was performed, 0.5-1 ml of lidocaine (1%) was used subcutaneously as local analgesic to facilitate an accurate injection of the joint. Patients were advised not to perform any sport activities within 2 days after the injection. All patients were treated unilaterally. Follow-up evaluations were performed at 7, 15 and 27 weeks after the (first) injection. Medication for pre-existing conditions was permitted, in addition to: acetaminophen (4 g/day) except on the day before, and the day of, follow-up visits; analgesics and NSAIDs with a clearance time of <8 h for pain other than OA
in the study ankle, or for post-injection pain management but not for more than three consecutive days or more than 10 days per month, nor on the day before, or the day of, a study visit; aspirin (325 mg/day) for anti-thrombotic prophylaxis, topical corticosteroids for skin problems, except at the study ankle, inhaled corticosteroids for asthma and allergic disease; non-pharmacological therapy (e.g. physical therapy) if begun at least 3 months before study entry.

Prohibited medications were: analgesics and aspirin except as described above; COX-2 inhibitors; oral corticosteroids; corticosteroid injections in any joint; topical analgesics at the study ankle; oral or parenteral anticoagulant therapy; glucosamine, chondroitin sulphate and diacerein, except if the patient was on a stable dose prior to inclusion and no changes to treatment were envisaged in the next 9 months. The use of all rescue and concomitant medications and therapies were recorded in the patient notes.

For this study Orthovisc® a high molecular weight HA preparation with a molecular weight of more than 1 million Da, was used. The recommended treatment for knee osteoarthritis consists of 3 injections of 2 ml once weekly. The study protocol, patient information and patient consent form were approved by the internal review board (Medical Ethical Committee of the Academic Medical Centre, Amsterdam).

Dosage

The choice for the dosages of 1 ml, 2 ml, 3 ml and 3 weekly 1 ml was based on our clinical experience. To minimize the risk of severe adverse reactions, the amount of injections was kept as small as possible and single dosages were preferred. The single dosages of 1 ml, 2 ml and 3 ml were chosen to determine whether the effect would depend on the dosage. Derived from the prescribed dosage for the treatment of knee osteoarthritis (3-5 weekly injections) the dosage of 3x1 ml was added to determine whether repeated injections would have comparable results.

Patient population

The study was open to patients of either gender presenting with OA pain in the ankle (‘study ankle’) at our outpatient clinic, ≥18 years of age with an active lifestyle and in general good health. Criteria for inclusion were: A clinical diagnosis of primary or secondary ankle OA.
A standard X-ray, taken within the 3 months prior to screening, confirming the clinical diagnosis and showing grade II OA (joint space narrowing with or without osteophytes, joint space narrowing ≤ 50%) according to the van Dijk et al. scale [7]; patient willingness to comply with any required washout period; no planned surgical intervention in the next 9 months. Patients had to score 20 or less out of 40 on the AOFAS pain score[8] for the study ankle.

Exclusion criteria were: Grade I or III talo-crural OA[7]; patients with post-traumatic OA if induced by trauma within the past 24 months; flare patients eligible for corticosteroid injection; chronic ankle instability; chronic anterior or posterior impingement syndrome in the study ankle requiring surgical treatment; current osteochondrosis dissecans in the study ankle; significant valgus/varus requiring corrective osteotomy; prior viscosupplementation in the study ankle; physical therapy if begun within the 3 months before study entry; history of sepsis in the study ankle; arthroplasty in the study ankle at any time, or any other surgery in the study ankle within the 6 months prior to study enrolment; clinically significant venous or lymphatic stasis in the study leg; any contraindication to acetaminophen; systemic or intra-articular injection of corticosteroid in any joint within the 3 months prior to enrolment; patients with related hypersensitivities to avian protein or any components of hyaluronan-based injection devices; concomitant inflammatory arthropathy; any history of, or active infection at the injection site; any significant chronic skin disorder at the injection site; any significant neuromuscular disease or musculoskeletal condition that would impede efficacy measurement; symptomatic peripheral vascular disease; current malignancy or treatment within the past 5 years; women who were pregnant or nursing, or women of childbearing potential not using a medically acceptable form of birth control; use of an investigational drug or device in the 90 days before entering the study or plans to use such a drug or device during the study; other factors assessed by the investigators that may limit the ability of the patient to perform necessary study evaluations.

Outcome measures

Safety: The safety assessment of Orthovisc® was based on reports of adverse events (AEs) collected between the signing of the informed consent form and the completion of the final follow-up visit for each patient. Study ankle and other (non-study ankle) AE
reports were collected at each visit.

**Efficacy:** Primary outcome measure for evaluating efficacy and determining dose dependency was ‘pain during walking activities’ measured with a 100 mm Visual Analogue Scale (VAS). Secondary outcome measures to evaluate efficacy and dose dependency were ‘pain at night and during the day while at rest’ measured with a 100 mm VAS, ‘general pain’ on a 4-points scale and the amount of rescue medication taken. Primary endpoint was at 15 weeks; secondary endpoints were at 7 and 27 weeks.

**Statistical analysis**

SPSS version 15.0 was used for statistical analysis. Non-parametric statistical tests were performed since sample sizes of the dose groups were small. Demographical data and baseline characteristics were compared to investigate differences at baseline between the randomised dose groups. The efficacy and dose effect of HA were determined by sub-group (dose group) analysis at each time interval. All outcome variables were defined as changes from baseline and analysed on a Last Observation Carried Forward (LOCF) basis. Statistical significance was determined at the p<0.05 level for all tests.

**Results**

**Patient population**

Twenty-seven consecutive patients participated in the study. One male patient was excluded from the study for violating the study protocol. The intention to treat population therefore consisted of 26 participants, 18 male and 8 female patients with a median age of 46 (range 21-84) years (Table 1).

Baseline characteristics (Table 2) were not equally distributed for VAS ‘pain during walking activities’ (Kruskal Wallis, p=0.04) and the severity score for ‘general pain’ (Chi-square, p=0.02). Other VAS-scores did not significantly differ between the dose groups (0.70<p<0.88).

Nine patients did not complete the study. These patients were asked for the reason of discontinuation. ‘No pain relief’ was reported by those patients (Table 3). Two patients were allocated to the 1 ml dose group, 4 of them were allocated to the 2 ml dose group,
1 to the 3 ml dose group and 2 to the 3x1 ml dose group. Since ‘no pain relief’ was an important reason for withdrawing from the study, analysis was performed per protocol “Last Observation Carried Forward (LOCF)” to avoid overestimation of treatment effects.

### Table 1: Demographics of the study population (n=26) per dosage group

<table>
<thead>
<tr>
<th></th>
<th>1 ml</th>
<th>2 ml</th>
<th>3 ml</th>
<th>3x1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (n)</strong></td>
<td>Male</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7 (100%)</td>
<td>7 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>(median, range)</td>
<td>31 (26-84)</td>
<td>47 (33-63)</td>
<td>51 (39-71)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>(median, range)</td>
<td>74 (60-83)</td>
<td>90 (65-110)</td>
<td>78 (65-93)</td>
</tr>
<tr>
<td><strong>Length (cm)</strong></td>
<td>(median, range)</td>
<td>174 (160-183)</td>
<td>174 (169-195)</td>
<td>179 (171-190)</td>
</tr>
</tbody>
</table>

### Table 2: Baseline values of primary and secondary outcome measures per dosage group

<table>
<thead>
<tr>
<th></th>
<th>1 ml</th>
<th>2 ml</th>
<th>3 ml</th>
<th>3x1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain at night (VAS, mm)</strong></td>
<td>(median, range)</td>
<td>21 (0-61)</td>
<td>45 (0-74)</td>
<td>15 (1-84)</td>
</tr>
<tr>
<td><strong>Pain during walking activities (VAS, mm)</strong></td>
<td>(median, range)</td>
<td>43 (7-71)</td>
<td>81 (46-100)</td>
<td>48 (24-87)</td>
</tr>
<tr>
<td><strong>Pain at rest (VAS, mm)</strong></td>
<td>(median, range)</td>
<td>21 (1-77)</td>
<td>44 (0-76)</td>
<td>54 (1-86)</td>
</tr>
<tr>
<td><strong>General pain (n, percentage)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (71%)</td>
<td>2 (19%)</td>
<td>4 (67%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (29%)</td>
<td>5 (71%)</td>
<td>2 (33%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

### Table 3: Reasons for discontinuation

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>No pain relief</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>No Discontinuation</td>
<td>17 (65%)</td>
</tr>
</tbody>
</table>
Efficacy

Primary variable

With the numbers available non-parametric Wilcoxon Signed Ranks tests of the dose groups separately, showed that 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) (Figure 1).

The VAS-scores of the 1 ml, 2 ml 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)(Figure 1). The median decrease from baseline at week 27 was 30 mm (Table 4). This change was not statistically significant (p=0.25; Table 4).
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### Table 4: Median change (range) of VAS-scores from baseline for pain during walking activities at week 7, 15 and 27 (LOCF)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Week 7</th>
<th>Week 15</th>
<th>Week 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml (n=7)</td>
<td>-7 (-35; 21)</td>
<td>1 (-58; 22)</td>
<td>6 (-22; 22)</td>
</tr>
<tr>
<td>2 ml (n=7)</td>
<td>-9 (-65; 13)</td>
<td>-7 (-97; 19)</td>
<td>-7 (-71; 19)</td>
</tr>
<tr>
<td>3 ml (n=6)</td>
<td>-6 (-39; 10)</td>
<td>-7 (-41; 2)</td>
<td>-7 (-87; 17)</td>
</tr>
<tr>
<td>3x1 ml (n=6)</td>
<td>-29 (-78; 7)</td>
<td>-47 (-78; 26)</td>
<td>-30 (-78; 26)</td>
</tr>
</tbody>
</table>

### Figure 2: Percentage of patients who improved at least one category on the general pain scale as compared to baseline.

Secondary variables

For ‘pain at night’ the decrease in pain was not significant at either the primary endpoint of 15 weeks, nor at the secondary endpoints of 7 and 27 weeks after the injection.

Median VAS-scores for ‘pain at rest’ showed a statistically significant decrease from baseline at both 7 weeks and 15 weeks in the 3x1 ml dose group (median 10 mm, p=0.046 at both time intervals). The changes from baseline at week 27 were not statistically
significant (p=0.35) for this dose group. The VAS-scores of the 1 ml, 2 ml, and 3 ml dose groups did not significantly change from baseline at all time intervals (0.17<p<0.87).

The variable ‘general pain’ was assessed as an ordinal 4-scale variable with categories (1) none, (2) mild, occasionally, (3) moderate, daily, and (4) severe, almost always present. The pain score for the 2 ml dose group did not improve at any time interval as compared to the baseline. In 2 out of 7 and 1 out of 6 patients in respectively the 1 ml and 3 ml dose group, the pain score had improved during the first 2 time-intervals. At the follow-up in week 27, no change was observed as compared to the baseline for these treatment groups. The general pain score for the 3x1 ml dose group had improved for 4 out of 6 patients at all time intervals (Figure 2). Chi-Square Tests showed a significant difference between the dose groups at week 27 (p= 0.001) in favour of the 3x1 ml dose group, since no improvement was observed in other dose groups.

Rescue medication

At baseline, six patients used rescue medication. Two of them used doses of respectively six to seven tablets and two tablets acetominophen(500 mg) per day and continued using the same dosages during the study at all time intervals. Both patients belonged to the 2 ml dosage group. The other four patients used very low dosage acetominophen(less than 2 tablets per day) at baseline and did not use any pain medication anymore after the 7 weeks follow-up. These patients were distributed over the 1 ml (n=1), 2 ml (n=1) and 3x1 ml (n=2) dosage groups.

Safety

Adverse events were reported by 7 (27%) patients. One patient in the 1 ml dose group, four in the 2 ml, one in the 3 ml, and one in the 3x1 ml dose group. The adverse reactions mostly occurred shortly after the injection and consisted of swelling and increased pain in the injected ankle joint, sometimes associated with increased local temperature. Most of them were mild or moderate in severity and resolved within 3 days. One patient (dose 3x1 ml) experienced severe pain and diffuse swelling of the ankle for about a week after the first injection. These symptoms resolved without any intervention. This patient received his second and third injection one week later than planned to have the adverse reaction resolved before the next intra-articular injection would take place.
Discussion

This study was performed to investigate the efficacy and safety of different dose regimens of intra-articular HA injections in the osteoarthritic ankle joint, in order to establish the ideal dose regimen. More patients are needed to confirm our results. Hyaluronic acid injections nowadays are commonly used in clinical practice for the treatment of knee osteoarthritis[9]. Increasingly the use in other joints is advocated (e.g. hip, ankle and shoulder)[1-5,10 and11]. For some brands dose finding studies for usage in the knee were performed and published[9,12]. Interestingly enough for other joints often the same schedule that has been advocated for the knee is used, no literature is present how these recommendations were made and how the decisions were made to use that same dosage regimen for different joints[1-5,10,11].

The ankle joint is much smaller than the knee and has a different shape. It is likely that less Hyaluronic acid is necessary to be effective in a smaller joint. The underlying study was undertaken to determine the correct dosage regimen for hyaluronic acid in the ankle joint.

Since infection is a possible hazardous side effect of intra-articular injections, one of our goals was to look for the smallest number of injections. The number of injections is also interesting for cost-benefit analysis.

The results suggest that intra-articular injections of the ankle joint with HA result in pain reduction, with superior results for the 3x1 ml regimen compared to single dosages of 1 ml, 2ml and 3 ml. Most apparent improvement was observed for the primary outcome measure 'pain during walking activities' (Table 4). Additionally, in the 3 x 1ml, categorical analysis of the 4-point scale of 'general pain' showed that the number of patients who experienced improvement was major compared to that of the single dose groups at all time intervals, though not always statistically significant. Nonetheless it needs to be emphasized that in this 3 x 1ml injection group still no more than 67% (4/6) of the patients had a beneficial effect of the injections.

In this study the dropout percentage was high (Table 3) (35%), the main reason was lack of pain relief (56%), and it can be assumed that the other four patients were disappointed about the results they got as well. Drop out occurred mainly in the single dose groups (7/9), two patients in the 3 x 1ml discontinued (2/6).
In the single dose groups pain relief seems only temporary with only a small decrease of most of the VAS-scores. This study was designed single blinded so the placebo effect of the injection cannot be ruled out completely, this is another reason to interpret these results with caution.

Our results are comparable to results of the treatment of the osteoarthritic knee. Weiss and Band (1995) reported that repeated injections were found to be required to maintain clinical improvement and injections of larger unit dosages were not found to bring supplementary relief [13].

Clinical studies showed that HA is most effective in the early course of the osteoarthritic process [14-16]. In our study Orthovisc® only seemed to be effective in the 3 x 1 ml group, a group that consisted mainly of patients (67%) that graded their pain at baseline as moderate (Table 2), severe pain as present in the 2 ml group (71%) might be associated with a more severe osteoarthritis and therefore be a reason for less pain relief after injection. However all patients were diagnosed radiographically with a grade 2 osteoarthritis.

Another point to take into consideration is the fact that different hyaluronic acids could give different results, since they have a different composition.

The observed adverse reactions to the HA injections correspond with those reported in the literature in which a temporary increased swelling and pain were reported as frequently observed adverse events [9,10,14]. Whether the adverse reactions in this study were due to the injection itself or the material is not clear, since in literature, the same adverse reactions were reported for both HA and saline injections in the knee [17-20]. The severe pain and swelling in one patient were probably caused by the failed injection.

The mean prevalence of adverse reactions as found in this study (transient pain and swelling at the injection site) was reported between 2 and 4% of the injections in controlled clinical trials of the knee joint [12] with some exceptions of 27%[21], 23%[20], and 47%[18].

In this study, 27% of the patients reported adverse events, which is comparable to the results of Salk et al. They reported transient pain at the injection site in 29% of the patients [2]. This relatively high occurrence of adverse reactions could be attributed to a more difficult application of intra-articular injections in the ankle joint than in the knee joint [18]. Other authors already emphasized that the occurrence of adverse events in knee
studies seemed to be influenced by the injection technique\textsuperscript{[15,22]}.

Since all adverse events resolved within a few days without intervention, the safety of intra-articular Orthovisc\textsuperscript{*} injections in the ankle joint seems to be acceptable.

In conclusion, the results of this study indicate that high molecular weight hyaluronic acid (Orthovisc\textsuperscript{*}) can be injected safely in the ankle joint and pain relief is observed with a 3 weekly dose regimen of 1 ml. The treatment shows potential to result in short-term (7 weeks) as well as long-term (27 weeks) pain reduction. This study showed no effectiveness for a single dose application for Orthovisc\textsuperscript{*}.

\textbf{Acknowledgement}

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References


