The conservative treatment of ankle osteoarthritis

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CHAPTER 4

The optimal injection technique for the osteoarthritic ankle: a randomized, cross-over trial

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Abstract

**Background:** To optimize the injection technique for the osteoarthritic ankle in order to enhance the effect of intra-articular injections and minimize adverse events.

**Methods:** Randomized cross-over trial. Comparing two injection techniques in patients with symptomatic ankle osteoarthritis. 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.

**Results:** Seventy patients fulfilled the study. The failure rate for both injection techniques was 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 didn’t show any difference between injection techniques.

**Conclusions:** There is no significant difference comparing the two injection methods regarding any of our formulated outcome measures. The use of contrast aided fluoroscopy for injecting the severe osteoarthritic ankle can be advised at all times.

**Keywords:** Osteoarthrits, Ankle, Injection technique, Hyaluronic acid.
Introduction

Hyaluronic acid and steroid injections are nowadays frequently used as part of the conservative treatment for the osteo-arthritis joint [1].

Adverse reactions besides poor efficacy of hyaluronic acid are mainly contributed to extra-articular placements [2-4].

Osteoarthritis might stiffen the joint and osteophytes might block the way of the needle which will make injecting the joint even more difficult. We treat patients with hyaluronic acid injections for more than 10 years now. Patients experienced a lot of different adverse events and a variable result in efficacy of hyaluronic acid [3,5]. This made us curious about how effective we are, injecting our patients intra-articularly. Two methods of injecting are used in our clinic; one using the injection technique that is commonly used for the ankle joint and one using a traction device that is commonly used for ankle arthroscopy [6,7]. The traction device is believed to open up the joint, which might facilitate the injection [7].

An optimization of the injection technique could possibly enhance the efficacy of our intra-articular injections and minimize the amount of adverse events.

The primary aim of this study was to investigate the accuracy of intra-articular injections in the osteo-arthritis ankle joint using the traction device compared to the injection technique that is commonly used for the ankle joint [6,7]. The secondary aim was to investigate the differences in the ease of the procedure, adverse events and patient reported outcomes.

Methods

Study design

This study was designed as a randomized cross-over trial with two treatment moments. Patients were recruited from our outpatient clinic. 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 randomized to one of two groups: group I first received an injection using the traction device, followed by an injection without traction a month later. Group II
received the injection without traction followed by the injection with the traction device. The dosing schedule was based on our study of the safety and efficacy of hylan G-F 20 (Synvisc®) in patients with symptomatic ankle (talo-crural) osteoarthritis \cite{3}. This study showed it is safe and effective to repeat the injection, in case of insufficient pain relief, after 1, 2 or 3 months. It was therefore decided, in order to test both injection techniques, to offer each patient two injections with one month interval. Injections were placed by one of the orthopedic surgeons (AW) according to a standardized protocol.

For randomization an online randomization program (www.randomizer.org) was used. Due to the clear differences in treatment modalities, neither patients nor the treating surgeon (AW) could be blinded. 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).

Patient population

The study was open to patients of either gender presenting with osteoarthritic pain in the ankle (‘study ankle’) at our outpatient clinic, ≥18 years of age in a general good health. Criteria for inclusion were: a clinical diagnosis of primary or secondary ankle OA confirmed by X-ray. Each X-ray was scored for the severity of osteoarthritis according to the van Dijk et al. scale \cite{8}. An indication for a hyaluronic acid injection was made at clinic visit by the orthopedic surgeon.

Exclusion criteria were: no knowledge of the Dutch language or not able to understand the study protocol; Patients who were allergic to contrast (Visipaque®); oral or parenteral anticoagulant therapy; clinically significant venous or lymphatic stasis in the study leg (edema); patients with related hypersensitivities to avian protein or any components of hyaluronan-based injection devices; concomitant inflammatory arthropathy; any history of, or active skin infection at the injection site; any significant chronic skin disorder at the injection site; symptomatic peripheral vascular disease; women who were pregnant or nursing, or women of childbearing potential not using a medically acceptable form of birth control.

Treatment

Both injections (with and without the traction device) were placed through the
anteromedial portal of the ankle joint as described for ankle arthroscopy using strict aseptic administration technique \(^9\). Before the HA injection was performed, 0.5–1 ml of lidocaine (1%) was used subcutaneous as local analgesic. Intra-articular placement of the needle was assumed if no resistance was felt when injecting some local anesthetic into the joint. A small amount (0.5-1ml) of contrast fluid (Visipaque\(^\text{®}\)) was injected by switching the syringe while holding the needle in place to determine the position of the needle on fluoroscopy. The X-ray beam was directed laterally. If the position was correct any fluid or effusion present in the joint was removed prior to the injection of 2ml of hyaluronic acid (Fermathon\(^\text{®}\)). If the position was not correct the needle was relocated and a small amount of additional contrast fluid injected until the position was found to be correct on X-ray. In case of an injection with traction, the non invasive ankle distraction device was applied after marking the injection site on the skin. Traction was applied after initial insertion of the needle after which the injection protocol was followed as would be in the injection without traction. The amount of traction was the same as in normal ankle arthroscopy and was applied for less than one minute. The second injection was performed by the same experienced physician who had administered the first injection (AW). This was done in the same manner using the other technique. Patients were allowed immediate full weight bearing when tolerated, but were advised not to perform any sport activities within two days after the injection.

Outcome measures

The primary outcome was the intra-articular needle positioning. The accuracy of the injection was determined by fluoroscopy. The location of the injected contrast was registered as either inside (success) or outside (failure) the joint (Figure. 1).

Secondary outcomes were:

- Ease of procedure defined as the amount of relocations of the needle needed by the orthopedic surgeon to assume that the needle was in the joint.
- The surgeon was asked how she experienced the injection procedure, this was registered in smooth, normal, difficult, extremely difficult.
- Adverse Events (AEs), for each injection procedure the type, location and duration of each local adverse event was recorded together with the amount and
type of rescue medication used by the patient to resolve these events. All patients were contacted by telephone one week after each injection to make inquiries for adverse events. In case of an adverse event this was repeated weekly until the adverse event resolved. The severity of any side effect experienced was registered using the 4-point scale, labeled as no side effects, mild (easily tolerated, caused minimal discomfort and did not interfere with everyday activities), moderate (caused sufficient discomfort to interfere with normal everyday activities), or severe (incapacitating and prevented normal everyday activities).

- Patient reported outcomes: pain during the injection; after each injection procedure each patient was asked to express the pain during the injection on a VAS score (0-100, 0 mm being no pain and 100 being extreme pain).
- Preference of injection technique; after the two injections each patient was asked which method he/she preferred and the reason why.

**Statistical analysis**

Sample size calculation was based on the primary end point (success rate). A difference of 20% of failure rates between the two methods was considered clinical relevant. Based on a power of 80% a two sided alpha of 0.05, a sample size of 70 patients was needed.

Statistical analysis was performed using SPSS 19.0 (IBM, Illinois 2011.) Due to skewed distributions, data were described as medians and ranges for continuous variables. Categorical outcomes were described as frequencies and percentages.

Prior to the main analysis in which the difference between the two injection modalities was evaluated, the presence of a carry-over effect and a period effect was assessed.

A carry-over effect implies that the effect of the first injection was still present when the patient received the second injection. This was assessed by analysing the difference in success rate between the two moments by use of a McNemar test.

The sequence (period) effects consider whether the impact of the injection was different when the order of the injections was changed. The period effect was assessed by comparing the difference in success rate between the two injection modalities in group I to the difference in success rate between the two injection modalities in group II, by use of a Mann Whitney U test.
Figure 1: Lateral view of the ankle. (A) shows contrast fluid inside the joint (success); (B) shows contrast fluid outside the joint (failure).
For the secondary continuous or ordinal outcomes (VAS, degree of difficulty, amount of injections), the carry-over effect was assessed by analysing the difference between the first and the second injection using a Wilcoxon Signed Ranks test. The period effect was assessed by analysing the absolute difference between injections with and without traction between group I and II using Mann Whitney U test. If a carry-over effect or period effect was present, the results of the second injection period were discarded from the analysis and only described per period.

For the main comparison of the two injection techniques, the difference in success rate between the two injection modalities was analysed using a McNemar test. Continuous and ordinal outcomes were analysed using a Wilcoxon Signed Ranks test. In case of period and carry over effects, non-paired chi-squared and Mann-Whitney U tests were performed for only the first injection group.

Correlations between continuous and ordinal outcome measures were calculated by use of Spearman correlation coefficients. Significance level of <0.05 was considered statistically significant.

Results

Patient population

Seventy from 72 randomized patients fulfilled the study (Figure 2). This group consisted of 40 male and 30 female patients (Table 1). Due to logistic reasons eight patients received the injection in inverse order and therefore changed Injection Groups (Figure 2). Finally, 27 (38%) patients had a primary injection with traction first and 43 (62%) without traction. Two patients in each group withdrew, both had a grade 2 Osteoarthritis (OA) (Figure 2). One female patient withdrew after an easy intra-articular injection with traction, due to persisting pain after the injection which lasted 14 days, this was graded as a severe adverse event. The other, male patient had an injection without traction which ended up being extra-articular. This patient sustained a possible allergic reaction after the injection (swelling and severe pain), lasting a couple of days and resolving with pain medication. It was graded as a moderate adverse event. This patient was advised not to receive a second injection. Since this is a cross-over study only patients that received both
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Injections could be analyzed statistically, therefore the results of these two patients were discarded from the analysis. However since these patients had to withdraw because of the occurrence of adverse events, their first injections were analyzed for these events.

**Figure 2: Composition of the two injection groups.**
Table 1: Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Total population N=70</th>
<th>Group I (traction-without traction) N=27</th>
<th>Group II (without traction-traction) N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (57%)</td>
<td>16 (59%)</td>
<td>24 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (43%)</td>
<td>11 (41%)</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.0 (18-68)</td>
<td>43.7 (18-68)</td>
<td>48.0 (19-68)</td>
</tr>
<tr>
<td>Side:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>38 (54%)</td>
<td>13 (48%)</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>Left</td>
<td>32 (46%)</td>
<td>14 (52%)</td>
<td>18 (42%)</td>
</tr>
<tr>
<td>Osteoarthritis grade (van Dijk):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>58 (83%)</td>
<td>21 (78%)</td>
<td>37 (86%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>11 (16%)</td>
<td>5 (18%)</td>
<td>6 (14%)</td>
</tr>
</tbody>
</table>

Table 2 shows the success rate of the injections in both techniques. The success rate in both the traction group and the group without traction was 76%.

An analysis was carried out of the first and last 15 patients to estimate the effect of a learning curve. Of the first 15 patients who were injected, 2/15 (13%) injections with traction were extra-articular compared to 5/15 (33%) without traction. Of the last 15 patients who were subjected to both injections, 2/15 (13%) of the injections in both the traction group and the group without traction were extra-articular. No significant learning curve was found (p=0.32).

<table>
<thead>
<tr>
<th></th>
<th>Injection with traction Injection N=70</th>
<th>Injection without traction Injection N=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate of injections</td>
<td>53/70 (76%)</td>
<td>53/70 (76%)</td>
</tr>
<tr>
<td>Ease of procedure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Normal</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Difficult</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Extremely difficult</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Number of attempts</td>
<td>2(1-8)</td>
<td>2(1-8)</td>
</tr>
</tbody>
</table>
Ease of procedure

No significant difference was found in the amount of attempts to place the needle into the joint between both techniques (p=0.18)(Table 2).

There was no significant difference in how either injection procedure was perceived by the orthopaedic surgeon (p=0.57)(Table 2). No significant relationship was found between the grade of osteoarthritis, the amount of attempts to get into the joint and how the injection was perceived by the surgeon with and without traction (0.24<p<0.94).

Adverse events

Forty-one patients (58%) experienced one or more adverse events after an injection with traction (Table 3). Ten injections were extra articular, there was no difference between the type of adverse events between the extra-articular group and the intra-articular group. Most adverse events were mild or moderate in severity and resolved by itself or by walking on crutches for several days or taking pain medication (acetaminophen or Nsaid’s) for a short period of time (less than 3 days).

Thirty-nine patients (55%) experienced one or more adverse events after the injection without traction, eight were extra-articular. There was no difference between the type of adverse events between the extra-articular group and the intra-articular group (Table 3). All adverse events resolved in a similar manner as mentioned above.

| Table 3. Types and Severity of Adverse events perceived after the injection |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Adverse events: Injection with traction 41/71 patients (58%) | Adverse events: Injection without traction 39/71 patients (55%) |
| Severity of AE | Mild | Moderate | Severe | Mild | Moderate | Severe |
|                | N=20 | N=16 | N=5 | N=25 | N=9 | N=5 |
| Types of adverse events and their frequency | | | | | | |
| Pain | 8 | 12 | 5 | 15 | 5 | 4 |
| Swelling | 7 | 9 | 3 | 11 | 5 | 3 |
| Stiffness | 0 | 2 | - | 0 | 1 | 1 |
| Redness | 1 | 3 | - | 0 | 0 | 0 |
| Other (cold, warm, instability) | 5 | 2 | - | 2 | 3 | 0 |
| Total | 21 | 28 | 8 | 28 | 14 | 8 |
Both groups had five patients that experienced severe adverse events. One of them was the patient that had to withdraw, as reported earlier. These AEs consisted of the same type of AEs as the mild and moderate group and they resolved in the same way as mentioned above (Table 3).

Patient reported outcomes

*Pain during the injection*: Due to the presence of a significant period effect and carry over effect (p<0.01) concerning the VAS pain score of the patients, the results of the second injection were discarded from the analysis. The pain caused by the first injection was not significantly different between the injections with traction (median 7, range 0-80) and without traction (median 12 range 0-64, p=0.88) (Table 4).

Grade 2 scored a significantly lower median VAS score of 9.5 (range: 0-64) compared to median 49 (2-60) for Grade 3 concerning the injections without traction (p=0.03). For the injections with traction the difference between Grade 2 (median 5 (0-80)) compared to Grade 3, (median 21 (5-75) was not statistically significant (p=0.18).

*Preference for either technique*: Patients were asked if they had a preference for either technique. Twenty-one (30%) answered no, twenty-six (37%) preferred without traction and twenty-three (33%) preferred traction.

| Table 4. Patient Reported Outcome: Pain (VAS 0-100mm) perceived during injection |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Group I                  | Group II        |
| N=28                       | N=27            | N=44            | N=43            |
| Injection 1               | Injection 2     |
| Traction                  | Without traction | Traction        |
| VAS Median (range)        | 7 (0-80)        | 16 (0-70)       | 12 (0-64)       | 32 (0-81)       |
| Subgroups                 |                 |                 |                 |                 |
| Grade 1 (N=1)             | N=1             | N=0             | N=0             |
| Grade 2 (N=60)            | N=22            | N=38            |
| Median (range)            | 5 (0-80)        | 9.5 (0-64)      |
| Grade 3 (N=11)            | N=5             | N=6             |
| Median (range)            | 21 (5-75)       | 49 (2-60)       |
Discussion

The present study evaluated the accuracy, the ease of the procedure, adverse events and patient reported outcomes of intra-articular injections in the osteoarthritic ankle joint using a traction device compared to the injection technique without traction that is commonly used in the ankle joint.

No optimal technique could be identified. Both injection techniques showed the same amount of failure rates (Table 2), 17/70 patients (24%). Due to the fact that joint opening could facilitate the intra-articular positioning of the needle we expected a higher success rate using the traction method. Different kinds of traction devices (invasive and non-invasive) are known to open up the ankle joint in patients under general and spinal anaesthesia. Joint opening up to 4.7 mm was described using an invasive distractor, a non-invasive distractor (the same as we used) created a joint opening of 4.3 mm in patients under anaesthesia [7,10]. Most of these were not suffering from osteoarthritis. Dowdy used a non-invasive distractor to examine 7 healthy volunteers, with 14 ankles. He measured, under permanent direct lateral fluoroscopically imaging, an increase from 3.1±0.5 mm to a mean of 4.2±0.6 mm [11]. We did not examine the joint space opening in this study. The arthritic joint might open up less which is a possible explanation for the same amount of failure rate.

The same five patients were initially injected extra-articular in both groups. Four had a grade 2 ankle OA (van Dijk) and one a grade 3. One of these grade 2 patients had a large osteophyte in the front of his ankle which was clearly visible on the lateral x-ray. The grade 3 patient had a very stiff ankle with a fixed plantar flexion of 10 degrees.

A lot of these injections would have been placed extra-articular, if not for contrast aided fluoroscopic control. Taking into account that patients in our study suffer from osteoarthritis, our failure rate is somewhat more positive than the failure rate Jones et al. showed; 24% vs. 33% [12]. However, our failure rate is still substantial and it seems advisable, in order to prevent failure of the injection in clinical practice, that more successful injection techniques will be investigated. Several suggestions have been made in literature to test placement of intra-articular injections using some alternative form of additional imaging. Bliddal et al. suggested fluoroscopically controlled mini-air arthrography, Glattes et al. hypothesized that a small amount of air added to an intra-articular knee injection can
confirm accurate placement by a squishing sound when moving the knee. In both studies the placement was also verified by post-injection radiographs \[2,13\]. Secondly, ultrasound guided injections are suggested in literature, however these injections have only been evaluated on cadaver feet without osteoarthritis \[14,15\]. The added value of these alternative modalities remains to be investigated.

At this moment the best way to inject the ankle joint is still with the aid of fluoroscopy. If fluoroscopy is not available, the use of a traction device can potentially increase the success rate. The results of our small sub analysis showed an improvement of 20% (33% to 13%) of the amount of intra articular injections in the last 15 patients compared to the first 15 patients whereas the amount remained the same for the injections with traction (13%). However this difference was not significant (p=0.32).

Despite the fact we know all our injections ended up being intra-articular, we still have a considerable amount of adverse events (Table 3). Hyaluronic acid was only injected after we proved that the contrast fluid was intra-articular. We certainly were critical and decided to register every unwanted side-effect, which might not be the case in other studies. Hyaluronic acid in itself is known to induce temporary benign side-effects like pain, swelling, warmth \[3,5,16-19\]. We have seen this before during our own research as well \[3,5\]. Possibly higher molecular weight hyaluronic acid induces more side effects \[16\]. Fermathron®, which we used, is a long chain molecule with a weight between 0.5-1.8X10\(^6\) Da, this is considered a low molecular weight. At this point no clear explanation has been found for the relatively high incidence of adverse events \[18-21\].

As for patient reported outcomes, patients were more painful at the second injection than at the first, hence the carry-over effect. This is a phenomenon we frequently observe in our daily practice. Possibly this is created by the injected hyaluronic acid at the first time point. An injection of hyaluronic acid stimulates hyalocytes to produce larger chains of hyaluronic acid. These hyalocytes are synovial-lining cells. The stimulated synovial membrane might be painful on injection \[22\].

Patients with severe osteoarthritis (grade 3) seem to tolerate traction better, however it is only a small group of 11 patients (Table 4), so no real conclusions can be drawn. They indicated less pain compared to an injection without traction. However these patients perceived more pain during either injection compared to the patients with grade 2 osteoarthritis (58 patients).
An explanation for the preference for traction in severe osteoarthritis can be sought in the discomfort that will be created compressing osteophytes and irritated synovium by dorsiflexion of the ankle in the case of an injection without traction, but again since this is just a small amount of patients no absolute recommendations can be made.

**Conclusions**

There is no significant difference between the two injection methods regarding any of our formulated outcome measures. Considering the substantial amount of possible extra articular injections prior to fluoroscopic control with both techniques, the use of contrast aided fluoroscopy for injecting the ankle with severe osteoarthritis, anterolateral or anteromedial osteophytes is advisable.

**Conflict of interest statement**

None of the authors has any conflict of interest to disclose.
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References


