Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up

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Abstract

Objectives
The goal of this study has been to determine whether hyaluronic acid (HA) or exercise therapy can improve functional parameters in patients with osteoarthritis (OA) of the ankle.

Methods
In a prospective clinical trial, 43 ankles (30 patients) with radiographic Kellgren Lawrence grade III OA were randomized to receive three intra-articular HA injections, with one-week interval of or exercise therapy for six weeks. Patients were evaluated by the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale and followed-up after 12 months.

Results
Total AOFAS Ankle-Hindfoot score of OA patients has improved in both groups, varying from 61.6±16.8 to 90.1±9.7 with HA treatment and from 72.1±16.6 to 87.5±17.5 using exercise therapy at the end of the trial (p<0.01). There were no statistically significant differences between the groups.

Conclusions
This prospective randomized trial confirmed that, both HA injections and exercise therapy provide functional improvement. However, larger trials with longer follow-up are necessary for more definite conclusions.

Key words
Osteoarthritis, ankle joint, hyaluronic acid, exercise therapy.
Introduction

The ankle joint is subjected to more weight-bearing force per square centimeter and is more commonly injured than any other joint in the body, but the prevalence of symptomatic arthritis at the ankle is approximately nine times lower than that at the knee and hip (1). Although uncommon, primary osteoarthritis (OA) of the ankle can cause significant impairment of function in otherwise healthy individuals (1). Conservative management, including analgesic non-steroidal anti-inflammatory drugs (NSAIDs), weight loss, exercise, physical therapy, orthotic devices and footwear modifications, activity changes and intra-articular corticosteroid injections are often effective, particularly in earlier stages of the disease (1-4). Apart from these treatment modalities, hyaluronic acid (HA) injections have put in to OA knee with varying degrees of success (5). A review of the literature revealed only two studies on the use of HA in OA ankle (6, 7), but neither has compared HA injections with other treatment options. In the present study we compared the effects of HA and exercise therapy in a prospective randomized study with a long-term follow-up.

Materials and methods

The series consisted of 43 ankles. Seventeen patients (26 ankles) had primary ankle OA and 13 patients (17 ankles) had secondary ankle OA of the defined by the clinical and radiographic findings, and all of them were seeking treatment. All patients with secondary OA of the ankle had definite history of severe trauma. None of the primary patients had rheumatoid arthritis. Additionally, all patients with primary OA had unil or bi-lateral involvement of the knees. The patients were classified as Kellgren Lawrence (7, 8) grade III OA with moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and sometimes deformity of bone contour. Any patient with radiographic appearance of definite deformity of bone contour was defined as Kellgren Lawrence grade IV OA and excluded from the study.

All patients were assessed with full medical examination and details of medication during the last year. Patients receiving NSAIDs were asked to discontinue this medication for the clinical trial. If not possible because of other diseases, then the patients were excluded from the study. Exclusion criteria included, inflammatory arthritis, previous intra-articular injections or any other invasive procedures in the ankle, significant comorbidity (renal, hepatic or heart disease), and chicken or egg allergy.

Patients were randomized by drawing lots using a computer program (Excel 2000) and 15 patients (19 ankles) were enrolled into HA group (group 1) and 20 patients (24 ankles) were enrolled into progressive ankle exercise (PE) therapy group (group 2). Details of randomization and follow-up are provided in Figure 1. Eight patients from group 1 were assessed as primary OA and seven patients as secondary OA. These values were nine and six for group 2, respectively.

The HA group received three injections of hyaluronic acid (Adant®, Na Hyaluronat, Erkim, Turkey) at 1-week intervals by the same physician. The dose of the HA was 2.5 mg in each injection. The injection was performed with the patient in half lying position with the knee flexed and the foot flat on the plinth. Then the anterior ankle joint line was palpated and the needle was inserted slightly upward in order to run upper surface of the talus which is slightly convex. When it was felt that the capsule was passed, then the joint fluid was aspirated if present, and then HA was injected (9). Patients were advised not to take part in strenuous activity for a few days.

The exercise program included a series of progressive, simple, isometric, isotonic range of motion, resistance, closed kinetic chain and proprioceptive exercises for six weeks. The exercise program was taught to the participants by two physical therapists and performed in home-based regimen. This means, patients came to the hospital at 1, 2, 3 and 6 weeks for learning the exercises. The details of exercise program are displayed in Table I.
Prior to the treatment, the ankle function of all patients was evaluated using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score (10) criteria that are based on a total of 100 points. A score of 100 points is possible in a patient with no pain, full range of sagittal and hindfoot motion, no ankle or hindfoot instability, good alignment, ability to walk more than six blocks, ability to ambulate on any walking surface, no discernible limp, no limitation of daily or recreational activities and no assistance devices needed for ambulation. Gait abnormality was categorized as none or slight, obvious or marked. Pain during activity and rest were evaluated with Visual Analog Scale (VAS).

All patients in both groups were evaluated at 1, 2, 3, weeks and 2, 3, 6, 12 months by a physical therapist who is blinded to the study. The study protocol was approved by the local ethical committee and all patients gave their informed consent.

**Statistical analysis**

The results of treatment were assessed during each patient visit. Changes with respect to baseline within treatment groups were assessed using Wilcoxon’s signed ranks test, and differences between treatment groups were assessed using Mann Whitney-U tests. Analysis of variance with repeated measures was applied to the efficacy data from the beginning of the study to 12 months of follow-up. A p value of <0.05 was considered significant. All data analyses were performed by using SPSS for Windows, version 10.0.

**Results**

The demographic data along with baseline disease characteristics at the

![Table 1. Description of the Progressive Ankle Exercises Program.](image)

<table>
<thead>
<tr>
<th>Week</th>
<th>Exercise</th>
<th>Length of time</th>
<th>Number of repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isometric exercises (ankle dorsiflexors, plantar flexors, invertors, evertors), Stretching exercises (gastro soleus, peroneal muscles and ankle dorsiflexor muscles), Active ankle range of motion exercises</td>
<td>Hold the contraction for 6 seconds and relax, To be done in 15 seconds, To be done in 6 seconds</td>
<td>10 repeat/ 3 times daily</td>
</tr>
<tr>
<td>2, 3</td>
<td>Isometric exercises (ankle dorsiflexors, plantar flexors, invertors, evertors), Stretching exercises (gastro soleus, peroneal muscles and ankle dorsiflexor muscles), Active ankle range of motion exercises, Strengthening exercises for ankle muscles, toe intrinsic muscles and quadriceps muscles</td>
<td>Hold the contraction for 6 seconds and relax, To be done in 6 seconds</td>
<td>8-10 repeat/3 times daily</td>
</tr>
<tr>
<td>6</td>
<td>Isometric exercises (ankle dorsiflexors, plantar flexors, invertors, evertors), Stretching exercises (gastro soleus, peroneal muscles and ankle dorsiflexor muscles), Active ankle range of motion exercises, Strengthening exercises for ankle muscles, toe intrinsic muscles and quadriceps muscles, Progressive resistive exercises for ankle muscles and quadriceps muscles, Proprioceptive exercises, Closed kinetic chain exercises</td>
<td>Hold the contraction for 6 seconds and relax, To be done in 6 seconds, To be done in 6 seconds</td>
<td>10 repeat/10 times daily</td>
</tr>
</tbody>
</table>
start of the trial are listed in Table II. Although demographic characteristics were similar, group 2 had significantly more total AOFAS Ankle-Hindfoot Score, and sagittal motion (Table II). Additionally group 1 had more difficulty in walking on uneven surface (Table II).

At the end of the study, all patients in both groups improved significantly as compared with the baseline values (Table III). This improvement was detected in all parameters listed in Table III except for sagittal motion. On the other hand, there was no significant difference between the groups at the end of the study.

Mean changes in each parameter during the study are displayed in Figures 2 and 3. Group 2 showed statistically less pain at activity at three weeks and better gait at 12 weeks (Fig 2). When compared between primary and secondary OA cases with respect to HA treatment or in relation to the exercise therapy, no differences were found.

Throughout the study no complications due to HA injection, such as pain, effusion, synovitis, haemarthrosis or septic arthritis were recorded.

Table II. Baseline characteristics of the 30 patients with osteoarthritis studied. Mean (SD).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (HA, n=15)</th>
<th>Group 2 (PE, n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.1 (11.3)</td>
<td>58.1 (12.1)</td>
<td>0.42</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.2 (7.1)</td>
<td>165.0 (7.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.9 (17.6)</td>
<td>75.5 (11.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>Gender</td>
<td>9/6</td>
<td>12/3</td>
<td>0.01</td>
</tr>
<tr>
<td>Pain during activity (VAS)</td>
<td>5.4 (2.1)</td>
<td>4.7 (2.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Pain at rest (VAS)</td>
<td>2.4 (3.0)</td>
<td>2.1 (2.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Activity limitation°</td>
<td>6.6 (2.4)</td>
<td>7.2 (2.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Walking distance°</td>
<td>2.7 (1.3)</td>
<td>2.6 (1.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Walking surface°</td>
<td>2.1 (1.7)</td>
<td>3.2 (1.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Gait abnormality°</td>
<td>5.6 (2.0)</td>
<td>5.8 (2.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Sagittal motion°</td>
<td>7.3 (1.4)</td>
<td>8.0 (0.0)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Total AOFAS Ankle-Hindfoot Score</td>
<td>61.6 (16.8)</td>
<td>72.1 (16.6)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

SD: Standard Deviation; HA: Hyaluronic Acid; PE: Progressive Ankle Exercises; VAS: Visual Analog Scale; AOFAS: American Orthopaedic Foot and Ankle Society.
°Graded by the AOFAS Ankle-Hindfoot Score.

Discussion

For symptomatic treatment of ankle OA, therapeutic options other than NSAIDs may benefit patients by decreasing the morbidity associated with the latter (1). Recently, it has been shown that OA of the knee can be effectively treated by the intra-articular injection of HA derivatives (5, 11-15).

Review of the literature revealed only two studies on the use of HA in ankle OA (6, 7), one evaluating the effects of HA opposite to placebo (6). On the other hand exercise and activity have been proven to be important factors in maintaining strength and flexibility, slowing the onset of debilitation in OA (3). So our study seems as the first comparing the results of exercise therapy with those from HA injections.

The results of current study indicate that patients with moderate OA of the ankle (Kellgren Lawrence Grade III) benefit either by three injections of HA or by 6 weeks of exercise therapy. In both groups the results after 12 months were statistically significantly different from the baseline values (Table III). The advantage of exercise therapy may be its noninvasive nature to be preferred both by the patients and the physicians; however, while exercise therapy lasts 6 weeks, HA injections stop at three weeks. This point may be advantageous for the preference of HA injections.

Although both groups in the present study improved in pain scores, walking surface, gait quality and total ankle-hind foot score (Table III, Figs. 2 and 3), we detected no difference in ankle motion. The explanation for these results may be the satisfactory range of motion in our patients at the beginning of the study. It is well known that 10° of dorsi fl exion and 20° of plantar fl exion is enough for activities of daily living (16). In our series both groups exhibited more degrees of motion. Additionally, the typical causes for decreased range of motion are limitation of muscle flexibility, pain, muscle guarding and decreased accessory joint mobility (2). The exercise therapy used in the present study affects the first three, but has no effect on the fourth which may be improved only by the mobilization techniques (2).
Fig. 2. Comparison of both groups throughout the study

- **Pain During Activity**
  - *p < 0.05

- **Pain at Rest**
  - *p < 0.05

- **Walking Surface**
  - *p < 0.05
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Fig. 2. Comparison of both groups throughout the study

d. Gait abnormality *p = <0.05

e. Sagittal motion *p = <0.05

Fig. 3. Mean according to the American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Score. *p = <0.05
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A review of the literature revealed only two studies on the use of HA in the ankle OA (6, 7). In the study of Salk et al., HA was investigated against placebo and the patients had been followed up for six months. They concluded that patients with OA of the ankle can successfully be treated with HA injections (6). Although our results are similar, we also showed that HA injections have no advantage over exercise therapy and these results did not deteriorate in the 12-month period. The study of Sun et al. is a prospective case series without any control group (7). However, the results of the authors are similar to ours, although they had injected HA in cases of OA ankles with grade I or II.

Although there are several potential complications derived from HA injections (17-27), we have observed none in the present series. Similarly, the other study on the same topic (6) had no complications. On the other hand, Sun et al. reported 6.7% of local adverse events but were healed spontaneously within 48 hours (7). However, it is essential to bear in mind the importance of full aspiration of any synovial fluid that may be present and meticulous attention to needle placement, in order to optimize efficacy and minimize adverse effects (28).

As a result, we conclude that both HA and exercise therapy are effective in alleviating the symptoms of OA and postponing definitive surgeries (total ankle replacement or arthrodesis) for 12 months, increasing the satisfaction levels of the patients. However, in our opinion, larger trials with longer follow-up and with cost effectiveness analyses are necessary for more definite conclusions.

References