Viscosupplementation of the ankle: A prospective study with an average follow-up of 45.5 months

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Accepted: 6 February 2013

Summary

Introduction: Providing pain relief for ankle osteoarthritis and delaying the need for a radical surgery procedure is difficult to achieve with analgesics that have limited efficacy or are not devoid of substantial side effects.

Hypothesis: The goals of this study were to evaluate the efficacy of viscosupplementation, explore which factors better predict Patient’s response and propose an injection protocol.

Materials and methods: Eighteen patients (26 ankles) with ankle osteoarthritis were included, with seven of them having received multiple series of injections. The average age was 60 years. Series of three injections, performed in the operating room under fluoroscopy-guidance, were evaluated after 4 and 12 months and then annually with the AOFAS score; patient satisfaction was also assessed.

Results: The average AOFAS score increased significantly from $61.8 \pm 15$ before the injections to $74.4 \pm 14.5$ and $73.7 \pm 16.6$ after 4 and 12 months, respectively. The average follow-up was 45.5 months and 73% of patients were satisfied or very satisfied. There were no adverse effects or intolerance. In patients receiving more than one series of injections, the average delay between series was 27.8 (range 15–43) months. Five patients had a radical surgery procedure after an average of 27 months of effective viscosupplementation.

Discussion: This prospective study showed that viscosupplementation had a significant positive effect ($P < 0.05$) in patients with ankle osteoarthritis when a three-injection protocol was used every two years on average. Neither etiology nor severity of the osteoarthritis was predictive of the response. In our opinion, fluoroscopy-guidance is essential for these injections.

Level of evidence: Level IV cohort study.

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http://dx.doi.org/10.1016/j.otsr.2013.02.008
Introduction

Although osteoarthritis (OA) in the ankle is not as common as in the knee or hip, it can be very painful and severely affect walking and activities of daily living [1,2]. Conservative management of arthritis pain must delay the need for radical surgery procedures such as fusion or joint replacement and limit the intake of NSAIDs.

Viscosupplementation, which consists of the intra-articular injection of hyaluronic acid (HA) in order to correct quantitative and qualitative changes in endogenous HA [3], seems to relieve the symptoms of osteoarthritis. Multiple studies have looked at the efficacy of viscosupplementation for knee osteoarthritis and have found mostly positive results [4–8].

HA has a visco-inductive effect in vitro: the addition of exogenous HA induces the synthesis of HA. This property is more apparent with high-molecular weight hyaluronic acid [9]. It contributes to its regeneration and limits interleukin-1 related inflammation [10–14]. It also has an analgesic effect [15–18] and a chondroprotective effect [19–21]. The HA concentration is 2–3 mg/ml in normal joints and is reduced to 0.8–2 mg/ml in joints of arthritic patients [22]. From a qualitative point of view, pathological HA molecules are 0.5 and 4.0 MDa (millions of Dalton) in size, versus 5.0 in normal cases [23]. In its altered state, HA contributes to inflammation [24] and no longer has lubricating and hydrophilic properties.

Viscosupplementation is an accepted treatment modality for knee osteoarthritis. But only a few clinical trials have evaluated its efficacy for treating ankle osteoarthritis up to now [25–30]. This study had three objectives: validate a three-injection treatment protocol, verify the efficacy of HA in the ankle and look for factors that are predictive of the response.

Materials and methods

Inclusion and exclusion criteria

The following inclusion criteria were used for the prospective series carried out from January 2003 to December 2009: patients presenting with Grade 1 or 2 talocrural osteoarthritis based on the Morrey and Wiedeman classification (Grade 0: normal ankle, Grade 1: small osteophytes and minimal joint narrowing, Grade 2: moderate osteophytes and moderate joint narrowing, Grade 3: significant narrowing with joint deformation or fusion), that had been progressing for at least one year and that was resistant to traditional conservative analgesic treatment [31].

Although concurrent medications were not recorded during the follow-up, the evaluation score took into account the occasional or continuous intake of analgesics.

Exclusion criteria consisted of a corticosteroid injection within the last month, systemic or local infection, coagulation problems, history of open fracture, known allergy to hyaluronic acid or associated conservative surgery procedure (arthroscopy, calcaneal osteotomy).

Viscosupplementation protocol

The treatment consisted of multiple injections from an ampule of high-molecular weight HA (Synvisc® 6000 kD, 2 ml) using a standardized technique. The protocol always comprised three injections, 15 days apart; this was considered as one series. The injections were always performed on an outpatient basis in the operating room using fluoroscopy system. No contrast product was used. The fluoroscopy allowed us to verify the needle position (Fig. 2). After mobilization of the ankle, full weight-bearing was allowed immediately, while advising the patient to get rest during the following days.

A new series of three injections could be repeated after the effect had worn off after a period of 12 months. Each series was considered as an independent parameter from a statistical point of view. In cases of treatment failure or no response to treatment, which was defined as a significant drop in the AOFAS score (below 40/100), a radical surgery procedure was proposed to the patient.

Analysis methods

The treatment efficacy was evaluated at 4 months, 12 months and then every year thereafter using the ankle...
functional score in the AOFAS and a four-level patient satisfaction scale (very satisfied, satisfied, disappointed or dissatisfied). The evaluation was performed by an independent evaluator. All adverse effects were evaluated. The patients were grouped by severity using the AOFAS functional score (stage I < 49/100; stage II 50 to 74/100; stage III > 75/100).

The change in the AOFAS score was analyzed using a paired Student’s t-test. Predictive factors were explored using ANOVA and Mann-Whitney Wilcoxon tests, with a significance threshold of $P < 0.05$.

**Results**

The average follow-up was 45.5 months (range 22.5–71.8), with no patients being lost to follow-up. No adverse effects were reported.

**Subjective effect of the injections**

Nineteen of the 26 injection series were evaluated as being satisfactory; seven were considered as disappointing with three leading to dissatisfaction. The average time elapsed between the series of two consecutive injections was 27.8 months (range 15–43).

**Change in the AOFAS score**

The average AOFAS score went from 61.8 ± 15.0 before the viscosupplementation to 73.7 ± 16.6 at 12 months after, with variations seen depending on the initial AOFAS grouping. The AOFAS scores are summarized in Table 1.

**Radical surgical treatment**

Of the 18 study patients, three failures were noted after the first series and two after the second series; the initial positive effect lasted for 24 months on average. Ankle joint replacement was proposed in three cases and talocalcaneal fusion in two cases. For these five patients, the average time between the first injection and this radical surgery was 27 months (range 10–43) (Table 2).

**Discussion**

We used a treatment protocol currently in use for the knee joint that consisted of three consecutive injections, 15 days apart. Other studies have used different methods [28–30] as shown in Table 3. In our opinion, use of this three-injection protocol is essential, as is fluoroscopy. Our study confirms the level I studies showing superiority of viscosupplementation over placebo for the ankle [26,28]. However, a recent level I study with high theoretical statistical power showed little difference relative to placebo [34]. But this study used a non-recommended, single-injection protocol with low molecular weight HA.

The main limitations of the current study are the small sample size, lack of a control group and lack of control over the oral analgesics taken by the patients. Nevertheless, the inclusion criteria were ankle osteoarthritis pain that had not been alleviated with common analgesics for at least one year.

**Table 1** Change in the overall AOFAS score by stage.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Before</th>
<th>4 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOFAS overall</td>
<td>61.8 ± 15</td>
<td>74.4 ± 14.5</td>
<td>73.7 ± 16.6</td>
</tr>
<tr>
<td>AOFAS stage I (n = 5)</td>
<td>40.2 (24–48)</td>
<td>56.2 (49–73)</td>
<td>60.8 (46–76)</td>
</tr>
<tr>
<td>AOFAS stage II (n = 17)</td>
<td>63.2 (51–74)</td>
<td>76.0 (47–98)</td>
<td>73.6 (43–97)</td>
</tr>
<tr>
<td>AOFAS stage III (n = 4)</td>
<td>83.2 (79–89)</td>
<td>90.2 (89–92)</td>
<td>90.2 (89–92)</td>
</tr>
</tbody>
</table>

**Table 2** Time before radical surgery and AOFAS score before the viscosupplementation for the five patients who failed treatment.

<table>
<thead>
<tr>
<th>AOFAS score before injection</th>
<th>Time before surgical treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>42.8</td>
</tr>
<tr>
<td>41</td>
<td>27.0</td>
</tr>
<tr>
<td>61</td>
<td>10.4</td>
</tr>
<tr>
<td>46</td>
<td>12.6</td>
</tr>
<tr>
<td>49</td>
<td>42.4</td>
</tr>
</tbody>
</table>

Figure 2  Fluoroscopy used to verify the intra-articular position of the needle before the injection.
Table 3  Overview of studies involving viscosupplementation treatment for ankle arthritis [32].

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Level</th>
<th>Country</th>
<th>Average age</th>
<th>Pts</th>
<th>Type</th>
<th>Fluoro</th>
<th>Outcome</th>
<th>Product</th>
<th>No. Inj</th>
<th>Interval</th>
<th>Comparison</th>
<th>Average FU (months)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucas y Hernandez et al.</td>
<td>2013</td>
<td>IV</td>
<td>France</td>
<td>60 ± 14.7</td>
<td>26</td>
<td>Case series</td>
<td>Yes</td>
<td>AOFAS</td>
<td>Synvisc®</td>
<td>3</td>
<td>15d</td>
<td>No</td>
<td>45.5</td>
<td>POS</td>
</tr>
<tr>
<td>Salk et al. [28]</td>
<td>2006</td>
<td>I</td>
<td>USA</td>
<td>58.8 ± 14.4</td>
<td>17</td>
<td>RCT</td>
<td>No</td>
<td>AOS pain</td>
<td>Hylan®</td>
<td>5</td>
<td>7d</td>
<td>Saline</td>
<td>6</td>
<td>POS</td>
</tr>
<tr>
<td>Cohen et al. [26]</td>
<td>2008</td>
<td>I</td>
<td>USA</td>
<td>49.8</td>
<td>28</td>
<td>RCT</td>
<td>Yes</td>
<td>AOS pain</td>
<td>Hylan®</td>
<td>5</td>
<td>7d</td>
<td>Saline</td>
<td>6</td>
<td>POS</td>
</tr>
<tr>
<td>Karatosun et al. [33]</td>
<td>2008</td>
<td>I</td>
<td>Turkey</td>
<td>55.1</td>
<td>30</td>
<td>RCT</td>
<td>No</td>
<td>AOFAS</td>
<td>Adant®</td>
<td>3</td>
<td>7d</td>
<td>PT</td>
<td>12</td>
<td>NEG</td>
</tr>
<tr>
<td>DeGroot et al. [34]</td>
<td>2012</td>
<td>I</td>
<td>USA</td>
<td>54.1 ± 14.5</td>
<td>56</td>
<td>RCT</td>
<td>Yes</td>
<td>AOFAS</td>
<td>Supartz®</td>
<td>1</td>
<td>N/A</td>
<td>Saline</td>
<td>3</td>
<td>NEG</td>
</tr>
<tr>
<td>Sun et al. [29]</td>
<td>2006</td>
<td>IV</td>
<td>Taiwan</td>
<td>50 ± 14.3</td>
<td>75</td>
<td>Case series</td>
<td>No</td>
<td>AOFAS</td>
<td>Supartz®</td>
<td>5</td>
<td>7d</td>
<td>No</td>
<td>6</td>
<td>POS</td>
</tr>
<tr>
<td>Witteveen et al. [30]</td>
<td>2008</td>
<td>IV</td>
<td>Italy</td>
<td>41 ± 12.3</td>
<td>55</td>
<td>Case series</td>
<td>No</td>
<td>AOS pain</td>
<td>Synvisc®</td>
<td>1 or 2</td>
<td>± 3 mo</td>
<td>No</td>
<td>9</td>
<td>POS</td>
</tr>
<tr>
<td>Mei-Dan et al. [27]</td>
<td>2008</td>
<td>IV</td>
<td>Israel</td>
<td>35.5 ± 14.2</td>
<td>15</td>
<td>Case series</td>
<td>No</td>
<td>AOFAS</td>
<td>Euflexxa®</td>
<td>3</td>
<td>7d</td>
<td>No</td>
<td>6</td>
<td>POS</td>
</tr>
<tr>
<td>Luciani et al. [35]</td>
<td>2008</td>
<td>IV</td>
<td>Italy</td>
<td>45 ± 15.9</td>
<td>21</td>
<td>Case series</td>
<td>No</td>
<td>AOS pain</td>
<td>Synvisc®</td>
<td>3</td>
<td>7d</td>
<td>No</td>
<td>18</td>
<td>POS</td>
</tr>
</tbody>
</table>

Inj: injections; RCT: randomized controlled trial; PT: physical therapy; FU: follow-up; Pts: number of patients; POS: HA had positive effect or was significantly better; NEG: HA was not significantly better than control.
Prospective study of ankle viscosupplementation

Viscosupplementation effect

The current study showed that viscosupplementation was effective against pain. Paradoxically, this effect was not correlated to the initial condition of the ankle. The pain had improved in 73.1% of cases. Nineteen of the 26 patients were satisfied or very satisfied with the treatment. The change in the AOFAS score showed that the treatment efficacy was extended significantly during the entire year after the injection series. This prolonged effect can be attributed to the anti-inflammatory action of hyaluronic acid, since its half-life in the joint is less than two days. This positive effect can be extended: 15 of the 26 cases were repeat treatments. Our results are comparable to the results of conservative surgery procedures (arthroscopic excision, curetage, microfracture, chondroplasty) that only partially and temporarily provide pain relief [36,37]. This work substantiates over ten years of clinical experience and provides objective evidence that viscosupplementation is a true treatment option for arthritic ankles.

Duration of the effect and predictive factors

Our study confirms the benefit for patients of this temporary analgesic treatment. The goal of using alternative treatments is to completely avoid if possible, or at least delay, the need for radical treatment. Viscosupplementation can be proposed no matter the etiology. However, the indication should only be made in patients with sufficient joint mobility (overall range of motion > 40°) and without large osteophytes that could hinder joint space clearance or make the injections difficult to perform, even with fluoroscopy.

In our series, the treatment efficacy extended to an average of 27.8 months, which is greater than the accepted protocol for the knee (repeated yearly). Our study found no significant relationship between the AOFAS score and the etiology of the OA or the progression of the OA. We did not find any factors that predicted a good response to this treatment. These factors are poorly defined [33,38,39]. As of now, there is no evidence to suggest that the treatment response is better as a function of the molecular weight of the hyaluronic acid for knee osteoarthritis pain, and as an extension, for the ankle [40–44].

In our opinion, one of the basic requirements is that injections be performed under fluoroscopy, to be sure the HA is being injected into the joint space. Only two studies have used this protocol [26,34]. We believe this procedure avoids the injection site complications found in other studies (inflammation and pain at the injection site) and ensures that good results will be achieved, as pointed out in many reviews on this topic [30,45,46].

Published reviews have shown the superiority of multiple HA injections versus placebo in Level I studies (pain, AOFAS score) and a positive effect in level IV studies (pain, AOFAS score), but not difference between HA and corticosteroid injections [46–48].

Conclusion

Our study confirms the efficacy of viscosupplementation using a protocol of three consecutive injections, 15 days apart for all patients with ankle osteoarthritis, no matter the etiology, having Grade 1 or Grade 2 disease according to the Morrey and Wiedeman classification. This effect was apparent at four months and was maintained out to 12 months; it became less marked after about 28 months on average. Also, since a certain number of patients eventually fail with this treatment, our study showed that this option delayed radical surgery by an average of 27 months.

The strong points of this study are the long follow-up, and that each patient had the option, if desired, to receive a new series of three injections if the first series was effective and the effect had faded (AOFAS score dropping below the initial AOFAS score).

When performed within certain prescribed limits (aseptic surgery conditions, fluoroscopy-guidance, three-injection protocol, use of high-molecular weight HA), viscosupplementation provides clear-cut and long-lasting pain relief that can be repeated as many times as necessary until a more radical surgery procedure is needed.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


