Comparison of two different molecular weight intra-articular injections of hyaluronic acid for the treatment of knee osteoarthritis

Gigis I1, Fotiadis E2, Nenopoulos A1, Tsitas K1, Hatzokos I1

12nd Orthopedic Department, G.Gennimatas General Hospital, Aristotle University of Thessaloniki, Thessaloniki
2Orthopedic Department, General Hospital, Veroia
Greece

Abstract
Background: Knee osteoarthritis (OA) is an incurable joint disorder, representing a major public health issue. Among options for symptom control, viscosupplementation with hyaluronic acid (HA) had established usefulness in pain and function improvement of the knee. However, it is not clear which form of HA yields better results.

Material and Methods: We compared two HA preparations with high (HMW) or low molecular weight (LMW) in terms of pain control and function improvement using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the visual analog scale (VAS) score in patients with knee OA. During 2013, 80 patients were enrolled in this prospective, double-blind, randomized study. Each patient received a weekly injection of either preparation with a total of five injections for the LMW group and three for the HMW group. They were evaluated at baseline, five weeks, three months and one year after treatment.

Results: In both groups, HA treatment resulted in significant improvement in pain and function that began immediately after treatment and lasted for one year. However when compared with each other, HMW and LMW groups were comparable in mean WOMAC, and VAS score at each time point. Neither preparation can interrupt disease progression as radiological findings remained constant during follow-up.

Conclusions: Intra-articular injections using HMW or LMW HA can improve stiffness, joint function and pain in patients suffering from knee OA. However, no clear benefit seems to exist between the two preparations and neither can slow disease progression. Hippokratia 2016, 20(1): 26-31

Keywords: Knee osteoarthritis, high molecular weight hyaluronic acid, low molecular weight hyaluronic acid, viscosupplementation

Corresponding Author: Ioannis Gigis, Assistant Professor of Orthopedics, 13 Profiti Ilia, 55535, Pylaia, Thessaloniki, Greece, tel: +306947301063, e-mail: jgigis@auth.gr
rheological properties and molecular weight of the preparation. Studies concerning the intra-articular use of HA with different molecular weight for the treatment of knee OA have been published over the last years with conflicting results, but possibly favoring high molecular weight HA. In this study, we compared the effectiveness of two HA preparations with different molecular weight, with regards to pain, functionality and joint’s width in patients with symptomatic knee OA.

**Material and Methods**

We conducted a prospective, double-blind, randomized study, comparing the efficacy of a high molecular weight (HMW) HA with a low molecular weight (LMW) HA preparation in patients with symptomatic knee OA regarding functional and clinical parameters.

In this study, we enrolled patients aged between 65-80 years, diagnosed with primary knee OA affecting one knee that attended the outpatient clinic of the 2nd Orthopedic Department of Aristotle University of Thessaloniki, during the year 2013. The study was approved by ethical committee of our institution and informed consent was obtained from each patient. According to radiologic findings, patients had to be stage II-IV on the Kellgren-Lawrence scale. Exclusion criteria were the diagnosis of rheumatoid arthritis or other inflammatory OA of metabolic origin, treatment with anticoagulants, previous knee infection in the previous six months and intra-articular injection of HA or corticosteroids in the past. Patients who had received physiotherapy in the previous year were also excluded from the study.

Efficacy of each preparation was evaluated using the visual analog scale (VAS) for pain following walking or home activity, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and x-ray imaging.

Pain VAS is a measurement instrument by which the patient expresses the intensity of pain perceived on a 10 cm scale, where 0 points represent no pain and 10 points (10 cm) extreme pain. Although highly subjective, it has been proved useful in the assessment of inflammatory or degenerative joint disease, as it is highly sensitive to even small changes in pain. It is also a simple tool that patients prefer; requires little training and is therefore widely used.

The WOMAC score is a validated multidimensional instrument assessing disability in patients with OA that has been used for over 20 years and is recommended as a measure of efficacy in osteoarthritis trials. It consists of questions assessing pain (five questions), stiffness (two questions) and physical function (17 questions). Scores range from 0 (worst) to 100 (best). A decrease in the mean WOMAC score is considered to indicate clinical improvement with treatment.

We also utilized X-ray imaging with the patient in standing position to evaluate joint space narrowing, a reliable marker of cartilage loss, using measurements of the medial and lateral knee joint space.

**Table 1**: Baseline characteristics of the study population consisting of 80 consecutive patients with knee osteoarthritis who were randomly assigned to two treatment groups and received weekly intra-articular injections either of low or of high molecular weight hyaluronic acid preparation.

<table>
<thead>
<tr>
<th></th>
<th>LMW group</th>
<th>HMW group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>25/15</td>
<td>23/17</td>
<td>0.648</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>67.38 (66-74)</td>
<td>67.20 (66-78)</td>
<td>0.509</td>
</tr>
<tr>
<td>Kellgren-Lawrence stage</td>
<td>2.55</td>
<td>2.57</td>
<td>0.814</td>
</tr>
<tr>
<td>WOMAC score</td>
<td>42.48 (SD 12.8)</td>
<td>43 (SD 13.54)</td>
<td>0.547</td>
</tr>
<tr>
<td>VAS score</td>
<td>7.18 (SD 3.84)</td>
<td>7.48 (SD 3.45)</td>
<td>0.707</td>
</tr>
<tr>
<td>Medial Joint Space (mm)</td>
<td>3.65 (SD 1.58)</td>
<td>3.66 (SD 1.37)</td>
<td>0.938</td>
</tr>
<tr>
<td>Lateral Joint Space (mm)</td>
<td>5.16 (SD 2.16)</td>
<td>5.17 (SD 2.07)</td>
<td>0.454</td>
</tr>
</tbody>
</table>

LMW: low molecular weight, HMW: high molecular weight group, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: visual analog scale, SD: standard deviation.

**Table 2**: Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale score, medial and lateral joint spaces at five weeks, three months and one year after treatment in the two groups of patients receiving either low or high molecular weight hyaluronic acid preparation.

<table>
<thead>
<tr>
<th></th>
<th>LWW group</th>
<th>HMW group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 weeks after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC score mean</td>
<td>23.8 (SD 9.4)</td>
<td>23.02 (SD 8.98)</td>
<td>0.333</td>
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<tr>
<td>VAS score mean</td>
<td>4 (SD 2.32)</td>
<td>4.1 (SD 2.39)</td>
<td>0.918</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC score mean</td>
<td>21.82 (SD 11.2)</td>
<td>20.75 (SD 12.76)</td>
<td>0.524</td>
</tr>
<tr>
<td>VAS score mean</td>
<td>3.2 (SD 1.8)</td>
<td>3.1 (SD 1.35)</td>
<td>0.617</td>
</tr>
<tr>
<td>1 year after treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC score mean</td>
<td>22.48 (SD 13.43)</td>
<td>21.93 (SD 14.79)</td>
<td>0.689</td>
</tr>
<tr>
<td>VAS score mean</td>
<td>4.35 (SD 1.54)</td>
<td>4.25 (SD 1.02)</td>
<td>0.861</td>
</tr>
<tr>
<td>Medial Joint Space mean</td>
<td>3.66 (SD 0.89)</td>
<td>3.66 (SD 1.26)</td>
<td>0.808</td>
</tr>
<tr>
<td>Lateral Joint Space mean</td>
<td>5.18 (SD 1.88)</td>
<td>5.18 (SD 2.77)</td>
<td>0.772</td>
</tr>
</tbody>
</table>

LMW group: low molecular weight group, HMW group: high molecular weight group, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: visual analog scale, SD: standard deviation.
In total, 80 consecutive patients, 48 females, and 32 males, aged 66-78 years, who met the inclusion criteria, were enrolled in the study. Patients were randomly assigned to two treatment groups, using random numbers charts. Forty patients, assign to the LMW group, received intra-articular injections with 5mg of hyaluronate sodium once a week for five weeks. In the other group, the HMW, the remaining 40 patients received intra-articular viscosupplementation with 5mg of HA once a week for three weeks. In all cases the same orthopedic surgeon, different from the principal investigator, performed the injections using the same technique. Patients were placed in lying position with the knee in 90° flexion, and the injection was performed after thorough disinfection of the skin using a scrub solution through the lateral arthroscopic portal.

Patients were evaluated at baseline, five weeks, three months and one year after the treatment using the parameters mentioned above. During their follow-up, patients were not allowed to receive analgesic medication or physical therapy. An independent, blinded evaluator assessed all the results from the two groups.

### Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) 22.0 (Version 22.0, Released 2013, IBM Corp., Armonk, NY, USA). Variables were tested for normality of distributions and equality of variances using the Kolmogorov-Smirnov and Levene’s tests, respectively. None of the variables had normal distribution and comparisons were made using non-parametric tests. Quantitative variables are described using mean values. Mann-Whitney U-test was used for comparisons between the two groups, and Wilcoxon test was used to assess values at baseline and after treatment. The level of statistical significance was set at p <0.05.
Results

The two groups were comparable for age, Kellgren Lawrence radiographic stage (p = 0.814), WOMAC score (p = 0.547), VAS for pain (p = 0.707) and medial and lateral joint space (MJS and LJS respectively) before treatment (p = 0.38, p = 0.54) (Table 1).

Five weeks after completion of treatment, there was no significant difference between the two groups in WOMAC (p = 0.333) or in VAS score (p = 0.918) using the Mann-Whitney U-test. The same observation was made three months after treatment for both WOMAC (p = 0.524) and VAS score (p = 0.617). At the end of the follow-up period, the two groups were still comparable in the two scores (p = 0.689 and p = 0.861 respectively) (Table 2, Figure 1, Figure 2).

In both groups, treatment with LMW and HMW HA preparation resulted in significant improvement in the WOMAC and VAS score during the follow-up period compared to baseline values. In all comparisons performed with Wilcoxon test, p-value was < 0.001. When comparing WOMAC and VAS score between three months and one year, we found increasing values in both of them but only VAS score was significantly worsened (Table 3).

Radiological findings of joint space narrowing as measured by medial and lateral space did not improve during one-year follow-up in either group of patients. For LMW group, the medial space p-value was 0.935 and for lateral 0.975. In the HMW group p-values were 0.741 and 0.974 respectively (Table 2, Table 3).

During treatment, we recorded no complications in either group of patients, so the procedure seems to be safe in this population.

Discussion

The aim of this study was to compare the effectiveness of two different preparations of HA, HMW and LMW, intended for intra-articular injection in patients with primary knee OA. In both groups, there was significant improvement in pain and knee function beginning early after treatment. This improvement had already begun five weeks after treatment and was maintained for one year. These results are in accordance with previous reports. According to Miltnner et al15, intra-articular injection of HA was effective and safe for treating patients with knee OA, as it resulted in decreased pain and functional improvement of the joint. Compared to placebo, in another trial conducted by Petrella et al, HA was more effective in improving pain and function measured with WOMAC and VAS scores16. This effect was the same using either a three or a six weeks schedule. This observation was further supported by other studies, all of them using five weekly intra-articular injections of HA in patients with knee OA15,17,18. HA has also proven effective in patients with ankle and hip OA19,20. The study concerning hip OA also compared two preparations with different molecular weight and found them to be equal in improving pain and function20.

The existence of HA with different molecular weight raises questions as to which preparation is better for patients with knee OA. We used an HMW and an LMW preparation according to manufacturer’s instructions. The two groups did not show any difference in WOMAC or VAS scores at any time after treatment during one-year follow-up. Also, during treatment no complication occurred in either group. Thus, we concluded that these two forms of HA are comparable with no significant adverse event. Our results point that both HA preparations can improve joint function and relieve pain shortly after completion of treatment and this result can last for at least one year. However, there was no difference between LMW and HMW HA. We can conclude that both treatment options are equally effective in managing symptoms in patients with knee OA.

Our results are supported by most of the trials published comparing different HA according to their molecular weight. Karlsson et al21 noticed clinical improvement during the first 26 weeks of treatment in two groups of patients treated with HA intra-articular injection, either HMW or LMW, but no difference between the two groups was found during one-year follow-up. The study also included a third group of patients treated with placebo with inferior results compared to pool HA treatment. This was, to our knowledge, the only previous study comparing the two preparations with a sufficiently long follow-up period. In another prospective study by Kotevoglu et al8, during a six-month period, patients treated with either HMW, LMW HA or placebo were evaluated using WOMAC score. Placebo was proved to be inferior to HA treatment. However, no clear benefit was found for either HA. Similar effects were also noticed by Lee et al in a trial that used the exact HA administration as used in our study22. During three-month follow-up results concerning pain and function evaluated with VAS and WOMAC scores were similar for both HA.

However, Wobig et al23 and Atamaz et al24, in their studies found that patients who received HMW HA had significantly better results on all primary outcome measures and overall assessment compared with those who received LMW HA. Administration schedule was the same for the two preparations, including one injection weekly for three weeks, in both studies, which is contrary to manufacturer’s instruction for LMW, as compared to our study where we used a five-week schedule.

A large number of reviews and meta-analyses has been performed during the past years comparing HA with different molecular weight, with confounding results. They all agree on the major heterogeneity in studies included with probable bias in their result. In all cases, HA is superior to placebo in symptom control. In a meta-analysis by Wang25, it was concluded that the intra-articular administration can decrease pain and function with or without activity and in another by Bellamy when compared to placebo, HA was found to be more effective1. When HA was compared to corticosteroids, it had a late-onset result but more durable1. In two reviews that favored the use of HMW HA, no firm conclusion could be established26,27.
This effect was attributed to chondroprotective, anti-inflammatory and analgesic properties of this preparation. On the other hand, a review by Coen found no superiority for either HA. These results were further supported by a large review by Reichenbach which included 2,085 patients with knee OA treated with HMW and LMW HA. Despite heterogeneity, no clear benefit was found, but HMW preparations were linked with more adverse events. In our study no adverse event was reported with either preparation.

Limitations of our study include the lack of a third group to be evaluated after use of placebo. However, infusion of saline into a knee with OA raises an ethical question as HA preparations are widely used and are proven to be safe and effective compared to placebo. Different treatment schedule for each preparation could be a bias of our study but to ensure a double-blind approach, patients were not aware of the difference between the two injections and the investigator had no knowledge of the schedule used for each patient. Only the surgeon who prepared and performed the injections knew which preparation was used for each patient. We performed no sample study calculation to strengthen our results because our original study was designed for a two-year period (one year for study enrollment and another for the follow-up period). We managed to enroll a total of 80 patients which we believe can produce remarkable results.

In conclusion, intra-articular injections of HMW and LMW HA improve stiffness, function and pain in patients with knee OA but these results seem equal no matter which preparation is used. Symptom control can last for one year. However HA has no impact on the development of the knee. J Rheumatol. 2006; 33: 946-950.

Conflict of interest
Authors report no conflict of interest.

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