



# Comparison of the Effects of Different Molecular Weight Hyaluronic Acid Application in Knee Osteoarthritis

## Diz Osteoartritinde Farklı Molekül Ağırlıklı Hyaluronik Asit Uygulamalarının Etkilerinin Karşılaştırılması

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### Abstract

**Objective:** The objective of this study was to evaluate the effect of different molecular weight (MW) hyaluronic acid (HA) application on pain and functional parameters in knee osteoarthritis (OA).

**Material and Method:** This study was designed as retrospectively. Hospital records of the patients who received intraarticular HA injection therapy in our center were screened. The patients were divided into 3 categories according to the MW of the preparates as the follows; Group 1: 0,6-1,2 Milyon Da of MW (N=26); Group 2: 1,1- 2,2 Milyon Da of MW (N=25); and Group 3: 1,7-2,1 Milyon Da of MW (N=25). All patients were assessed using Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) before the treatment and one month after the injection.

**Results:** A total of 76 patients (61 females, 15 males) with a mean age of 62,1 years (minimum-maximum: 50-70 years) were included. VAS and WOMAC scores did improve significantly in all groups (all for  $p<0.001$ ). However, no significant difference was observed between the groups in terms of the delta values of the VAS and WOMAC scores between the groups ( $p: 0,721$  and  $p: 0,595$ , respectively).

**Conclusion:** Significant reductions in VAS and WOMAC scores were observed in all 3 patient groups in our study. Yet, there was no significant difference regarding the MW of HA preparations.

**Keywords:** Knee osteoarthritis, hyaluronic acid, pain

### Öz

**Amaç:** Bu çalışmanın amacı, diz osteoartritinde (OA) farklı moleküler ağırlıklı (MA) hyaluronik asit (HA) uygulamasının ağrı ve fonksiyonel parametreler üzerindeki etkisini değerlendirmektir.

**Gereç ve Yöntem:** Bu çalışma geriye dönük olarak planlandı. Merkezimizde intraartiküler HA enjeksiyon tedavisi alan hastaların hastane kayıtları tarandı. Preparatların MA'sına göre hastalar aşağıdaki gibi 3 kategoriye ayrıldı; Grup 1: 0,6-1,2 Milyon Da MA (N=26); Grup 2: 1,1- 2,2 Milyon Da MA (N=25); ve Grup 3: 1,7-2,1 Milyon Da MA (N=25). Tüm hastalar, tedaviden önce ve enjeksiyondan bir ay sonra Görsel Analog Skala (VAS) ve Western Ontario ve McMaster Universities Arthritis Index (WOMAC) kullanılarak değerlendirildi.

**Bulgular:** Yaş ortalaması 62,1 yıl (minimum-maksimum: 50-70 yıl) olan toplam 76 hasta (61 kadın, 15 erkek) dahil edildi. VAS ve WOMAC skorları tüm gruplarda anlamlı olarak iyileşti (tümü için  $p<0,001$ ). Ancak gruplar arasında VAS ve WOMAC puanlarının delta değerleri açısından gruplar arasında anlamlı bir fark gözlenmedi (sırasıyla  $p: 0,721$  ve  $p: 0,595$ ).

**Sonuç:** Çalışmamızda her 3 hasta grubunda da VAS ve WOMAC skorlarında anlamlı düşüşler gözlemlendi. Ancak, HA preparatlarının MA'sı ile ilgili önemli bir fark yoktu.

**Anahtar Kelimeler:** Diz osteoartriti, hyaluronik asit, ağrı



## INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disorder primarily affecting the knee, increasing with age and being one of the major causes of physical disability in elderly populations.<sup>[1]</sup> Knee pain due to OA is a condition that should be highlighted because it is the most common physical disability in the elderly.<sup>[2,3]</sup> In the treatment of knee OA, different treatment modalities have been proposed to reduce pain, increase functioning, reduce disability, and reduce the progression of the disease. In this context, intraarticular hyaluronic acid (HA) is considered to be an effective non-surgical treatment for alleviating symptoms.<sup>[4-6]</sup>

Hyaluronic acid, a highly viscous polysaccharide, is seen in the extracellular matrix, soft connective tissue, synovial fluid, and articular cartilage. After synthesis in chondrocytes and synovial cells, HA is released into the synovial space and fills the cartilaginous spaces with the ligament.<sup>[7]</sup> The HA molecule, from the family of glycosaminoglycan (GAG), consists of thousands of repeating disaccharide units (N-acetylglucosamine and glucuronic acid) to form a high molecular weight (MW) (3-4 million dalton) polysaccharide chain. It occupies a large spherical area when fully hydrated.<sup>[7,8]</sup> In addition to its elastic and viscous qualities, HA's physical presence promotes an important role of joint synovial fluid in maintaining homeostasis and at the same time provides lubricity on the joint surface, shock absorption, elasticity, hydration, and nutrition. In long-term periods, HA reduces the inflammatory mediators leading to a chondroprotective effect.<sup>[7,8]</sup> HA preparations are available for intra-articular use in different MW. The low MW HA consists of long unbranched chains of chemically unmodified natural HA while the high MW HA consists of chemically modified and cross-linked HA chains. The effectiveness of intraarticular HA injections may depend on the viscoelastic properties of partially injected HA, and the viscoelastic property of HA is influenced by its MW. For this reason, it has been suggested that HA injection with higher MW initially may provide more clinical benefit. However, clinical trials do not support this data. Lo et al.<sup>[7]</sup> suggested that the results of a meta-analysis would be more effective with higher MW HA; but there is no definite result due to the heterogeneity of the included experiments. Results from OA's large animal models have shown that HA with MW of 0.5-1 million daltons is more effective in reducing synovial inflammation and recovering synovial fluid properties than high MW HA.<sup>[8]</sup> In addition, several preclinical studies evaluating the modification of joint structure in OA animal models have reported that medium and low MW HA is a better potential for disease modification because they can more easily access diseased tissue.<sup>[8]</sup> In conclusion, it is controversial to discuss the MW of HA in the current literature. For this reason, the objective of this study was to evaluate the effect of different MW HA application on pain and functional parameters in knee OA.

## MATERIAL AND METHOD

### Study Design

This study was designed as retrospectively. Effects of different MW HA application on pain and physical function in knee OA were compared. In this context, hospital records of the patients who received intraarticular HA injection therapy in the Department of Hacettepe University Medical School, Department of Anesthesiology and Reanimation, Algology Unit, between the January 2013 and December 2016 were screened. The screening was performed between the May 2017 and August 2017.

The study was carried out with the permission of Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: ....., Decision No: 2017-610). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Since the study was conducted retrospectively, it does not require to obtain written informed consent from the participants.

### Participants

- Patients who had knee OA according to the American College of Rheumatology diagnostic criteria
- >50 and <70 years of age
- Patients who did not receive intraarticular steroid or platelet rich plasma therapy
- To have persistent pain that did not respond to medical therapy or physical agents
- To have degenerative changes according to the radiographs

The patients were divided into 3 categories according to the MW of the preparates as the follows;

**Group 1:** 0,6-1,2 Million Da of MW (N=26)

**Group 2:** 1,1- 2,2 Million Da of MW (N=25)

**Group 3:** 1,7-2,1 Million Da of MW (N=25)

### Outcome Measures

All patients were assessed using Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) before the treatment and one month after the injection.

WOMAC is a valid and reliable measure and its use in the hip and knee OA is suggested by the Outcome Measures in Rheumatology Clinical Trials (OMERACT). WOMAC mainly consists of three main categories as pain, stiffness, and physical function (overall 24 items). Each item is scored as 0 to 4 according to the Likert Scale. The Turkish version of this scale which has been previously validated, was used.<sup>[9,10]</sup>

VAS is a measure of pain severity. It usually consists of a straight line with a length of 10 centimeters (100 mm), and the two most extreme definitions of the parameter to be evaluated are placed on both ends of the line. For example, the absence of an acute pain (0 mm on a straight line) for pain is recorded on the other end with the most severe pain (100 mm on a straight line) and the patient marks his/her condition on a straight line.<sup>[11]</sup>

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA) was used for the statistical analyses. Descriptive data are shown as mean, standard deviation, median, minimum-maximum, count or percentage. Pre-test and post-test comparisons were made using Paired-t test after checking the normal distribution. Between-group analyses were made using One Way Anova. A p value of 0.05 was accepted as significant.

### RESULTS

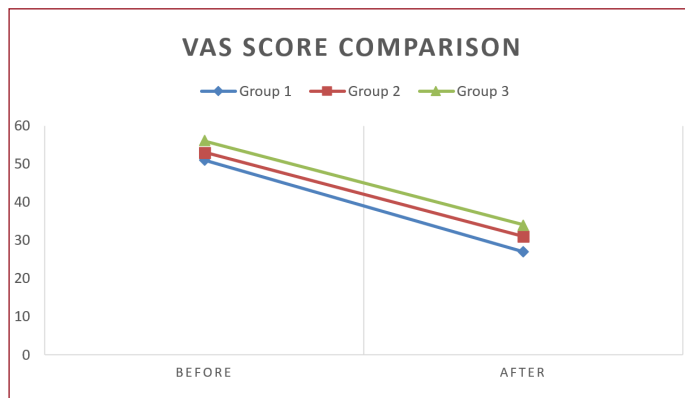
A total of 76 patients (61 females, 15 males) with a mean age of 62.1 years (minimum-maximum: 50-70 years) were included.

Baseline and post-treatment VAS and WOMAC scores of the groups are shown in **Table 1**. VAS and WOMAC scores did improve significantly in all groups (all for  $p < 0.001$ ). However, no significant difference was observed between the groups in terms of the delta values of the VAS and WOMAC scores between the groups ( $p: 0.721$  and  $p: 0.595$ , respectively) (**Figure 1** and **Figure 2**).

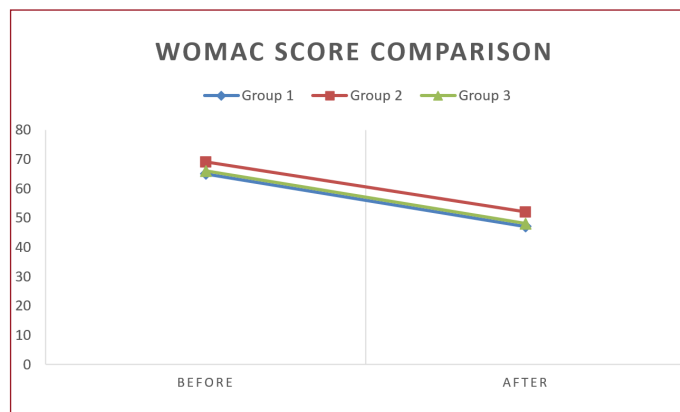
**Table 1. Baseline and after-injection VAS and WOMAC scores**

Variables	Baseline	After Treatment	p value
Group I			
VAS	54.4±2.36	32.80±3.77	p <0.01
WOMAC	65.44±2.83	47.72±3.78	
Group II			
VAS	53.07±2.31	31.15±3.70	p <0.01
WOMAC	69.03±2.77	52.84±3.71	
Group III			
VAS	55.6±2.3	32.80±3.77	p <0.01
WOMAC	66.64±2.83	48.48±3.78	

Pre-test and post-test comparisons were made using Paired-t test after checking the normal distribution. Between-group analyses were made using One Way Anova. A p value of 0,05 was accepted as significant.



**Figure 1.** Graph shows the delta values of the groups regarding the VAS Scores



**Figure 2.** Graph shows the delta values of the groups regarding the WOMAC Scores

### DISCUSSION

Intraarticular administration is a very long-standing pharmacological treatment approach in many treatment guidelines for the treatment of OA. In this sense, intraarticular HA injection has been applied for over 25 years. Currently, intraarticular HA therapy is recommended by the International Osteoarthritis Research Society (OARSI) with the level of evidence Ia (meta-analysis of randomized and controlled trials) by the European League Against Rheumatism (EULAR) as category II- A (at least one controlled trial without randomization). Intraarticular HA injection is increasingly used due to satisfactory results and lower risk for complications. As such, HA injection is a good alternative treatment method to treat persistent pain in patients with renal or other systemic diseases, previous history of gastrointestinal problems, and polypharmacy.

We aimed to explore the effects of different MW HA applications on pain and functional parameters in knee OA. Although the three groups showed significant improvement, no significant difference was observed between the groups. In our study population, most of the participants (80%) were female and the mean age was 62.1 years. Female gender, compared to the males, has been previously reported as a risk factor for OA.<sup>[13,14]</sup> In addition, the age ranged from 50 70 in our study. OA rate increases with age, and age has been previously accepted as a risk factor in many studies.<sup>[15]</sup> Jarvholm and colleagues<sup>[16]</sup> found that the incidence of knee OA significantly increased with age between 50 and 75 years; but a limited increase over the age of 75. When the average age of the patients participating in the study is considered, it is seen that there is more advanced age disease in accordance with the studies conducted by OA.

In patients with knee OA, the effectiveness of intraarticular HA has been demonstrated in many controlled and observational clinical trials in alleviating pain and improving joint function. Roughly, intraarticular HA placebo-controlled studies have shown decreased pain and increased functional capacity, which were observed 1 week after the first injection

and lasted from 3 weeks to 6 months. In these experiments, injections were made with several preparations of HA once every 3-5 consecutive weeks, and in some studies, analgesic treatment was allowed together.<sup>[17]</sup> In our study, three injections were made for one week of HA for all three MWs, and three of which were found to be effective on pain and WOMAC, and our results are compatible with the literature.

The concept of MW of HA applied has gained importance in recent years, and studies on HA products with different MWs have appeared in the literature. The most important factor in introducing this concept was that there were no differences in the MWs of HA products in some in vitro and in vivo studies. Tobetto et al.<sup>[18]</sup> examined the effects of HA products of different MW and concentration on neutrophil-mediated cartilage destruction. Therefore, three different HA preparations with different MWs were used and as a result, the product with high MW was significantly more effective than the products with low MW in reducing GAG loss. Coleman et al.<sup>[19]</sup> showed that the HA product with a MW of 2.2 million daltons in the animal OA model can pass 75% of the product with MW of 0.5 million daltons, while only 20% of synovial fluid from the synovial fluid passes through the synovial tissue and the product with lower MW have penetration power. Nonetheless, changes depending on the MW of HA are not clearly understood.<sup>[20]</sup> Lo et al.<sup>[21]</sup> have investigated the seven different HA preparations in their meta-analysis whereby high MW HA preparations are more effective than low MW HA preparations. But they also highlighted the difficulties in interpreting the results due to heterogeneity between studies. Arrich et al.<sup>[22]</sup> did not reveal any difference in the effects of HA preparations with different MWs in their systematic review and meta-analysis. In our study, the effects of three different preparations with different MWs were parallel to each other, and there was no significant difference between the groups.

### Limitations

The retrospective design, lack of demographical and clinical features such as body mass index, diabetes mellitus and other comorbidities, severity of the OS are the limitations of this study.

### CONCLUSION

Significant reductions in VAS and WOMAC scores were observed in all 3 patient groups in our study. Yet, there was no significant difference regarding the MW of HA preparations. HA preparations of different MW can also be used in OA associated knee pain and provide a significant reduction in the patient's knee pain and a significant improvement in the patient's physical function. However, since there is no significant difference between the three preparations compared to the pain of the patient and the effect on the physical function, it is appropriate to select the most cost-effective preparation by evaluating the cost

in terms of which preparation is preferred. Side effects and complications of intra-articular HA are negligible, and it can be concluded that the application is safe.

### ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: ....., Decision No: 2017-610).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author has no conflicts of interest to declare.

**Financial Disclosure:** The author declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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