ORIGINAL ARTICLE

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

Gigis I[1], Fotiadis E[2], Nenopoulos A[1], Tsitas K[1], Hatzokos I[1]

[1]2nd Orthopedic Department, G.Gennimatas General Hospital, Aristotle University of Thessaloniki, Thessaloniki
[2]Orthopedic 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 begun 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

Introduction

Osteoarthritis (OA) is a joint disorder that primarily affects the knee and its prevalence increases with age, representing the leading cause of disability in older populations[1]. There is no cure, but many approaches exist in order to control symptoms like pain or stiffness and improve patients' quality of life. One treatment option widely utilized, is the intra-articular injection of either corticosteroid or hyaluronic acid (HA)[2]. Corticosteroid mechanism of action is based on the reduction of inflammation, ameliorating pain and disability, but with only a short-term benefit and raising concerns about side effects after its long-term use[3].

Native HA is a glycosaminoglycan with high molecular weight found mostly in the extracellular matrix of many tissues[4]. It is a major component of the synovial fluid that promotes viscoelasticity and helps to protect articular cartilage and adjacent soft tissues. OA correlates with reduction of HA found in the synovial fluid, resulting in lower elasticity and viscosity. Viscosupplementation by injection of exogenous HA into the synovial joints aims at restoring the normal rheological environment and has been established as an effective treatment option[5]. According to a meta-analysis of 40 different controlled trial, it has been proven that HA injections significantly reduce pain in knee OA[3].

HA preparations available for intra-articular use differ on their molecular weight. The low molecular weight preparations (0.5-1.5 million Dalton) can achieve maximum concentration into the joint and are thought to reduce inflammation, however, they present lower elastoviscosity than native HA[6]. High molecular weight preparations (6-7 million Dalton) result in a better increase in fluid retention into the joint and possibly present with stronger anti-inflammatory effect[7]. Efficacy might be related to the

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.

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

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

rheological properties and molecular weight of the preparation[8]. 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[9-11]. 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[12].

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[13,14].

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 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.

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

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.

Table 3: Changes in Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale score, medial and lateral joint spaces during follow-up in comparison to baseline in each group of patients receiving either low or high molecular weight hyaluronic acid preparation.

	LMW group	HMW group
5 weeks after treatment		
	Baseline/Five weeks	**Baseline/Five weeks**
WOMAC score	42.48/23.8 (p <0.001)	43/23.02 (p <0.001)
VAS score	7.18/4 (p <0.001)	7.48/4.1 (p <0.001)
3 months after treatment		
	Baseline/ Three months	**Baseline/Three months**
WOMAC score	42.48/21.82 (p <0.001)	43/20.75 (p <0.001)
VAS score	7.18/3.2 (p <0.001)	7.48/3.1 (p <0.001)
1 year after treatment		
	Baseline/One year	**Baseline/One year**
WOMAC score	42.48/22.48 (p <0.001)	43/21.93 (p <0.001)
VAS score	7.18/4.35 (p <0.001)	7.48/4.25 (p <0.001)
Medial Joint Space	3.65/3.66 (p =0.935)	3.66/3.66 (p =0.741)
Lateral Joint Space	5.16/5.18 (p =0.975)	5.18/5.19 (p =0.974)
	3 months/One year	**3 months/One year**
WOMAC score	21.82/22.48 (p =0.576)	20.75/21.93 (p =0.496)
VAS score	3.2/4.35 (p =0.004)	3.1/4.25 (p =0.002)

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

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.

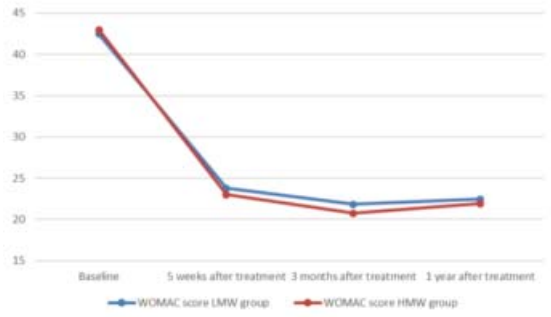

Figure 1: Changes in Western Ontario and McMaster Universities Osteoarthritis Index score during one year follow-up in the two groups of patients receiving either low or high molecular weight hyaluronic acid preparation.
LMW group: low molecular weight group, HMW group: high molecular weight group, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

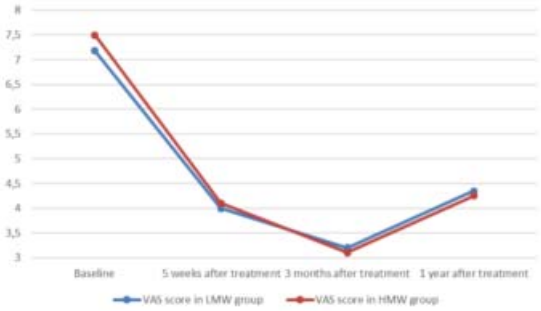

Figure 1: Changes in visual analog scale score during one year follow-up in the two groups of patients receiving either low or high molecular weight hyaluronic acid preparation.
LMW group: low molecular weight group, HMW group: high molecular weight group, VAS: visual analog scale.

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-Smirnoff 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 worsen (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 post treatment and was maintained for one year. These results are in accordance with previous reports. According to Miltner et al[15], 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 scores[16]. 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 OA[15,17,18]. HA has also proven effective in patients with ankle and hip OA[19,20]. The study concerning hip OA also compared two preparations with different molecular weight and found them to be equal in improving pain and function[20].

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 al[21] 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 an another prospective study by Kotevoglu et al[8], 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 study[22]. During three-month follow-up results concerning pain and function evaluated with VAS and WOMAC scores were similar for both HA.

However, Wobig et al[23] and Atamaz et al[24], 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 Wang[25], 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 effective[3]. When HA was compared to corticosteroids, it had a late-onset result but more durable[3]. In two reviews that favored the use of HMW HA, no firm conclusion could be established[26,27].

This effect was attributed to chondroprotective, anti-inflammatory and analgesic properties of this preparation[27]. On the other hand, a review by Colen found no superiority for either HA[28]. These results were further supported by a large review by Reichenbach[29] 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 at least one year. However HA has no impact on the disease, as medial and lateral joint spaces remain constant during follow-up. Further studies are needed to examine the maximum duration of each form of HA, to ensure comparable results during a longer period.

Conflict of interest

Authors report no conflict of interest.

References

1. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987; 30: 914-918.
2. Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. J Bone Joint Surg Am. 2003; 85-A: 1197-1203.
3. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006: CD005328.
4. Maus U, Andereya S, Gravius S, Siebert CH, Ohnsorge JA, Niedhart C. Lack of effect on bone healing of injectable BMP-2 augmented hyaluronic acid. Arch Orthop Trauma Surg. 2008; 128: 1461-1466.
5. Richette P, Chevalier X, Ea HK, Eymard F, Henrotin Y, Ornetti P, et al. Hyaluronan for knee osteoarthritis: an updated meta-analysis of trials with low risk of bias. RMD Open. 2015; 1: e000071.
6. Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol. 2006; 33: 946-950.
7. Migliore A, Giovannangeli F, Granata M, Laganà B. Hylan g-f 20: review of its safety and efficacy in the management of joint pain in osteoarthritis. Clin Med Insights Arthritis Musculoskelet Disord. 2010; 3: 55-68.
8. Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006; 26: 325-330.
9. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage. 2011; 19: 611-619.
10. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012; 157: 180-191.
11. Sun SF, Hsu CW, Hwang CW, Hsu PT, Wang JL, Tsai SL, et al. Hyaluronate improves pain, physical function and balance in the geriatric osteoarthritic knee: a 6-month follow-up study using clinical tests. Osteoarthritis Cartilage. 2006; 14: 696-701.
12. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011; 63 Suppl 11: S240-S252.
13. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988; 15: 1833-1840.
14. Salaffi F, Leardini G, Canesi B, Mannoni A, Fioravanti A, Caporali R, et al. Reliability and validity of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2003; 11: 551-560.
15. Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis--a prospective clinical trial. Osteoarthritis Cartilage. 2002; 10: 680-686.
16. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006; 33: 951-956.
17. Miltner O, Schneider U, Siebert CH, Wirtz DC, Niethard FU. [Measuring isokinetic force in patients with gonarthrosis before and after hyaluronic acid therapy]. Z Orthop Ihre Grenzgeb. 2001; 139: 340-345.
18. Schneider U, Miltner O, Graf J, Thomsen M, Niethard FU. [Mechanism of action of hyaluronic acid in gonarthrosis of both knee joints in a right/left comparison. Study with dynamometry, oxygen partial pressure, temperature and Lequesne score]. Z Orthop Ihre Grenzgeb. 1997; 135: 341-347.
19. Chang KV, Hsiao MY, Chen WS, Wang TG, Chien KL. Effectiveness of intra-articular hyaluronic acid for ankle osteoarthritis treatment: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2013; 94: 951-960.

20. Tikiz C, Unlü Z, Sener A, Efe M, Tüzün C. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. Clin Rheumatol. 2005; 24: 244-250.
21. Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 2002; 41: 1240-1248.
22. Lee PB, Kim YC, Lim YJ, Lee CJ, Sim WS, Ha CW, et al. Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial. J Int Med Res. 2006; 34: 77-87.
23. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. Clin Ther. 1999; 21: 1549-1562.
24. Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006; 26: 873-878.
25. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am. 2004; 86-A: 538-545.
26. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. JAMA. 2003; 290: 3115-3121.
27. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. Am J Sports Med. 2015: pii: 0363546515609599.
28. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. BioDrugs. 2012; 26: 257-268.
29. Reichenbach S, Blank S, Rutjes AW, Shang A, King EA, Dieppe PA, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum. 2007; 57: 1410-1418.