



Original Article

Therapeutic efficacy of three hyaluronic acid formulations in young and middle-aged patients with early-stage meniscal injuries

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Abstract. [Purpose] To investigate and compare the efficacy of three hyaluronic acid formulations in patients with early-stage meniscal injuries. [Subjects and Methods] Male and female patients who were admitted to our clinic between January 2013 and December 2013, diagnosed with early-stage meniscus lesions of the knee, and given a hyaluronic acid treatment were included in this retrospective study. Patients were categorized into 3 groups according to their treatments: MONOVISC, OSTENIL PLUS, or ORTHOVISC. Scores from a Visual Analog Scale and the Western Ontario and McMaster Universities Arthritis Index were evaluated at baseline and one, three, and six months after baseline. [Results] A total of 55 patients were included in this study. Most of the patients were female (55%), and the mean age of the patients was 42.4 (\pm 8.1) years. Based on the pre- and post-injection data, there was significant reductions both in the Visual Analog Scale score and the Western Ontario and McMaster Universities Arthritis Index score after the injections for all groups. According to intergroup comparisons, no significant difference was observed in terms of efficacy. [Conclusion] Three hyaluronic acid formulations produced a similar efficacy in patients with meniscal injuries, and further studies are needed to evaluate long-term results.

Key words: Hyaluronic acid, Comparison, Meniscal injury

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INTRODUCTION

Menisci are composed of fibrocartilage tissues and have various functions in knee articulation. Meniscus injuries are one of the most frequent problems that orthopedic surgeons encounter^{1, 2)}. The number of patients who are treated with arthroscopy due to meniscus lesions increases in conjunction with increased age and weight³⁾. It is especially difficult to understand whether the pain of osteoarthritis (OA) patients is caused by an unstable meniscus or by OA. In addition, degenerative rupture of the meniscus may be either a result or effect of knee OA, and it has been incidentally detected in magnetic resonance imaging (MRI) tests of patients who have painful knee OA⁴⁾.

Conservative treatment options include physiotherapy, intra-articular (IA) injections of hyaluronic acid (HA), steroids, and platelet-rich plasma injections. Most patients use these conservative treatment options for years. Meniscectomy is mostly applied in cases in which conservative treatment is not useful.

HA is a glycosaminoglycan with polysaccharide and is necessary for normal articular homeostasis. In OA, the concentra-

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tion of HA and its molecular weight in synovial liquid decrease^{5, 6}). In young patients, IA HA injections are useful in the short term and may reduce OA progression. HA has anti-inflammatory, anabolic, and chondroprotective effects—these effects have been determined to be useful in in-vitro studies and treatment of meniscus and anterior cruciate ligament (ACL) lesions in animal models. According to results obtained from various clinical studies and data obtained from patient series, IA HA injections are useful for acute knee injuries when isolated ACL damage is seen with symptomatic meniscus tears and cartilage damage⁷).

HA products are categorized according to their molecular weights: low molecular weight (between 0.5 and 1×10^6 Daltons [Da]), medium molecular weight (2×10^6 Da), and high molecular weight (6×10^6 Da)⁸). HA preparations with low molecular weight (LMW) are applied in three or five doses weekly, each containing 2–2.5 ml HA^{9, 10}. HA preparations with high molecular weight (HMW) are applied in one dosage of 4–6 ml¹¹).

During the manufacturing of HA preparations, various adjuvant molecules (mannitol, sorbitol, and chondroitin sulfate) are added to prolong their effect. Clinical effects of HA products with various features have not been completely identified, and the superiority of one product over another has not been exactly determined¹²). OSTENIL PLUS[®], MONOVISC[®], and ORTHOVISC[®] are the three most frequently used HA treatments in our clinic. OSTENIL PLUS[®] contains 2.0% fermented sodium hyaluronate and has a LMW of 1.6 million Da. Each bottle is 2 ml and contains 10 mg mannitol, which helps stabilize HA chains by acting as an antioxidant and prolonging the effects of HA on articulation^{13–15}). MONOVISC[®] has a light, cross-linked molecular weight (approximately 2.5 million Da). It contains 22 mg HA/ml and is 4 ml in total¹⁶). ORTHOVISC[®] has a HMW of 1.0–2.9 million Da and is an ultra-pure, natural hyaluronan dissolved in physiological saline. The hyaluronan is extracted from rooster combs¹⁷).

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale is a self-administered, disease-specific, health-related quality of life instrument that asks patients to answer questions concerning the studied knee and hip. The WOMAC has a total score and scores for three subscales: pain, stiffness, and physical functioning. For every question on the WOMAC, participants rate their pain, stiffness, or physical function using five ordinal responses: none, mild, moderate, severe, and extreme. Higher scores indicate worse pain, stiffness, and functional limitations¹⁸). The Visual Analog Scale (VAS) evaluates patients' pain levels on a scale of 0–10, with 0 being no pain and 10 being the most intense pain.

The primary objective of this study was to evaluate the effect of three HA products on patients who have early-stage meniscus damage (grade 1–2 degeneration). The secondary objective was to evaluate and compare the pain and functional states of the patients by using VAS and WOMAC.

SUBJECTS AND METHODS

Male and female patients who were admitted to our clinic between January 2013 and December 2013, diagnosed with early-stage meniscus lesions (grade 1 or 2 on the Kellgren Lawrence scale) of the knee in the tibiofemoral compartment, and given HA treatment with back-flow injection were included in this retrospective study—the clinic must also have had available data for these patients for the past 6 months. The following were defined as exclusion criteria for patient enrollment: having no MRI, late-stage meniscus damage, contraindication for IA injections, inflammatory joint disease, previous IA fracture of the knee, allergy to any substance related to the study medication, renal impairment, or metastatic tumors.

The same physiatrist administered the HA injections, and patients were categorized into 3 groups according to their treatments: Group I (MONOVISC[®], single dose), Group II (OSTENIL PLUS[®], single dose) and Group III (ORTHOVISC[®], three doses, at one-week intervals). Identical case report forms were used to record patient data. These forms included sections for demographic data, physical examination results, and inclusion/exclusion criteria. Additionally, all treatments, adverse events, VAS, and WOMAC scores were recorded in these case report forms. VAS and WOMAC scores were evaluated at the baseline and one, three, and six months after the baseline visit.

Various methods are used for injecting HA treatments, and one of the most frequently used is the back-flow technique¹⁸). Since it is safer, all patients in the present study were injected using the back-flow technique, applying our clinic's routine practice methods for the technique. The articulation and area to be injected were wiped with sterile cotton while the patient laid in a supine position. The route of application from the lateral was relieved by pressing on the patella medial. Then, 1 cc of lidocaine and 4 cc of sterile saline solution were drawn into a 21 G, 5 cc syringe. The knee joint was entered laterally, parallel to the patella. One half cc was given from the mix and the physiatrist controlled whether the liquid was returned. After ensuring that the mix was in the articulation, the HA bottle was applied. After the injection, applied liquid was dispersed by moving the knee in flexion-extension movements¹²).

This study was conducted in accordance with the Declaration of Helsinki and approved by Istanbul Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee with approval number KA EK/2014/2. Verbal and written informed consents were obtained from all patients included in this study.

Mean, standard deviation, median, minimum-maximum, ratio, and frequency values were used for descriptive statistics. The Kolmogorov-Smirnov test was used to observe data dispersion. The ANOVA and Kruskal-Wallis tests were used to analyze the quantitative data. A χ^2 test was used to analyze the qualitative data. All data analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

Table 1. Baseline characteristics, treatment information, VAS and WOMAC scores of the patients

		Minimum–Maximum	Median	Mean ± SD	/n - %
Age (years)		24–58	42	42.4 ± 8.1	
Gender	Female			41	74.50%
	Male			14	25.50%
Occupation	Housewife			29	52.70%
	Employed			22	40.00%
	Self-employed			3	5.50%
	Teacher			1	1.80%
Treatment	Group I			15	27.30%
	Group II			24	43.60%
	Group III			16	29.10%
VAS Score				41	
Baseline		8–9	8	8.2 ± 0.4	
1st month		2–7	2	2.9 ± 1.5	
3rd month		1–7	2	2.9 ± 1.6	
6th month		1–7	2	2.8 ± 1.4	
WOMAC Score					
Baseline		82–110	96	95.2 ± 5.4	
1st month		24–96	37	44.7 ± 24.6	
3rd month		24–96	31	42.7 ± 25.5	
6th month		24–96	26	30.9 ± 17.3	

SD: standard deviation; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Table 2. Per group evaluation of patient demography, VAS and WOMAC scores at baseline and follow-up visits

		Group I			Group II			Group III		
		Mean ± SD	/n - %	Median	Mean ±SD	/n - %	Median	Mean ±SD	/n - %	Median
Age		44.6 ± 7.5		47	43.3 ± 7.8		43	38.9 ± 8.6		38
Gender	Female	12	80.0%	17		70.8%	12	75.0%		
	Male	3	20.0%	7		29.2%	4	25.0%		
VAS Score										
Baseline		8.2 ± 0.4		8	8.3 ± 0.5		8	8.2 ± 0.4		8
1st month		3.8* ± 2.2		2	2.4* ± 0.5		2	2.9* ± 1.3		2
3rd month		3.7* ± 2.3		2	2.4* ± 0.9		2	2.8* ± 1.4		2
6th month		3.5* ± 2		2	2.4* ± 0.9		2	2.6* ± 1		2
WOMAC Score										
Baseline		96.1 ± 0.4		96	94 ± 8.1		96	96 ± 0		96
1st month		49.6* ± 30.7		48	40.4* ± 13.8		37	46.6* ± 30.9		24.5
3rd month		51.5* ± 30.8		52	37.7* ± 14.1		37	41.9* ± 32		24
6th month		26.3* ± 1.8		26	24.6* ± 0.9		24	44.6* ± 28.1		29

*Significant when compared to baseline (Wilcoxon test, $p < 0.05$), SD: standard deviation; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

RESULTS

A total of 55 patients were included in this study. Most of the patients were female (55%), and the mean (\pm standard deviation) age of the patients was 42.4 (\pm 8.1) years, ranging between 24–58 years. Almost half of the patients (43.6%) received OSTENIL PLUS[®] treatment and were allocated in Group II (Table 1). The age and gender distribution of the patients in Groups I, II, and III did not differ significantly ($p > 0.05$) (Table 2).

The VAS values did not differ significantly ($p > 0.05$) among the three groups, either at the baseline or one, three, or six months after the treatment. The VAS values decreased significantly ($p < 0.05$) in all three groups in the first, third, and sixth months when compared to the baseline (Table 2). In terms of absolute change in VAS scores compared to the baseline, the highest numerical change was observed in Group II; however, this change was not significantly higher than the other groups ($p > 0.05$). Since mean VAS scores were the same (2.4 points) for Group II in months one, three, and six, the absolute change did not differ in follow-up visits (Table 3).

Similar to the VAS score, the WOMAC total score also did not differ among groups ($p > 0.05$) either at the baseline or at follow-up visits conducted one, three, or six months after initiation of treatment. Within the groups, the WOMAC total score

Table 3. Mean absolute changes in VAS and WOMAC scores at follow-up visits comparing to baseline

	Absolute change		
	Group I	Group II	Group III
VAS score			
1st month compared to baseline	4.4	5.9	5.3
3rd month compared to baseline	4.5	5.9	5.4
6th month compared to baseline	4.7	5.9	5.6
WOMAC score			
1st month compared to baseline	46.5	53.7	49.4
3rd month compared to baseline	44.6	56.4	54.1
6th month compared to baseline	69.8	69.4	51.4

VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

decreased significantly ($p < 0.05$) in all three groups in the first, third, and sixth months compared to the beginning of the study (Table 2). Numerically but not significantly highest absolute change in WOMAC score compared to the baseline was detected in Group I during the sixth month visit (69.8 points). Similar absolute change was observed in Group II with a 69.4 point reduction in sixth month (Table 3).

DISCUSSION

Menisci play a significant role in the structure of the knee joint. Their role includes providing power transmission, shock absorption, joint stability, lubrication, and proprioception^{19, 20}. Injury of the meniscus causes degenerative changes in the knee joint. Biomechanics studies have determined that compressive overload on the knee joint is transmitted to the menisci when extending at least 50%²¹.

Surgically repairing meniscus damage has always been controversial and the success of surgical meniscus treatment strategies is limited. After meniscectomy, the degree of OA development is in direct proportion to the amount of meniscus resected⁷. According to the results of another study conducted by Moseley et al., no clinical difference was found in the treatment results of those patients who received arthroscopic debridement and those who received the sham²². Especially when gender distribution, patient selection, and treatment options are considered, it is not clear how to identify patients' benefit from arthroscopic debridement²³. For example, a study by Fabricant et al. showed that female patients and those with advanced OA have worse prognoses for arthroscopic meniscectomy²⁴.

A study by Vermesan et al. found that few OA patients who received arthroscopic debridement for degenerative medial meniscus tears benefited from IA steroid injections in the short term²³. For non-surgical treatment, or maintenance treatment following surgery, IA HA injections may also be considered.

Within this scope, we aimed to evaluate the efficacy of three different HA formulations in patients with early-stage meniscal degeneration who had not received surgical treatment. The present study is the first national study to assess the efficacy of three HA products with different molecular weights and features in patients with early-stage meniscal degeneration. In our study, effectiveness of the three HA products were evaluated using VAS and WOMAC scores. This study obtained positive, meaningful results in all three groups. Intergroup comparison observed no superior product. All three products were considered effective since they reduced VAS and WOMAC scores significantly, beginning 1 month after the initiation of the treatment.

In a prospective study conducted by Miltner et al., similar improvements were obtained, in terms of VAS scores. In this study, intra-articular injections (5 injections, 1 injection per week) of 20 mg HA were administered to Kellgren Lawrence grade II–III, male and female patients ($n=43$) with a minimum age of 50. Study results revealed that HA treatment was effective and safe for treating patients with knee OA based on VAS and Lequesne scores, obtained 1 day prior to the first injection and 1 week after the final injection²⁵.

In another prospective study conducted by Petrella et al., HA treatment was compared to placebo. Treatment with 20 mg/ml HA injection once weekly over 3 weeks was more effective in improving pain and function measured with WOMAC and VAS scores²⁶.

There have been trials published comparing different HAs according to their molecular weight, such as LMW and HMW. Clinical improvement was noticed in both patient groups receiving HMW or LMW HA injections, but no difference was observed between the HMW and LMW treatment groups during the 1 year follow-up. In the same study, a third group was treated with placebo, and this group was found inferior to both HMW and LMW treatment groups²⁷. The HA injection trials, to our knowledge, have a follow-up period of 6–12 months. In an example of a prospective trial with a 6-month follow-up period conducted by Kotevoglou et al., patients were treated with either HMW HA, LMW HA, or placebo and were evaluated using WOMAC scores for pain, stiffness, and function. As expected, the placebo proved to be inferior to HA treatment,

but no clear benefit was found for either type of HA²⁸). In both reports, HMW and LMW HA formulations had comparable efficacy outcomes. VAS and WOMAC scores are often used to evaluate the treatment outcomes of HAs in clinical trials and controversial results are also reported with LMW and HMW treatments. In studies reported by Wobig et al. and Atamaz et al., HMW HA treatment groups had significantly better results compared to those who received LMW HA treatments. In our study, two groups received LMW HA treatment and one group received HMW HA treatment, all presenting comparable efficacy outcomes^{29, 30}).

The radiological grade of OA, IA treatment with or without surgery, patients' age and gender, IA administration schedule, HA molecular weight, or treatment evaluation scoring systems were different from each other in many studies. The major heterogeneity seen in all studies included probable bias in their own result, nonetheless, we noticed HA has always been superior to the placebo in symptom control.

Since this study was conducted on available retrospective patient data, it was not possible to compare our results with a placebo group—therefore we recognize this as a limitation to our study. Additionally, it was not possible to prohibit patients from using analgesics or non-steroid anti-inflammatory drugs.

In conclusion, according to the WOMAC and VAS scores, all three HA preparations were effective in treating early-stage meniscus injuries. We recommend the use of HA injections combined with other treatment methods, including orthoses and exercise, to treat meniscus damage or degeneration. In addition, new data related to the long-term efficacy of IA HA needs to be collected in studies conducted with young patients who have meniscus damage.

REFERENCES

- 1) Paletta GA Jr, Manning T, Snell E, et al.: The effect of allograft meniscal replacement on intraarticular contact area and pressures in the human knee. A biomechanical study. *Am J Sports Med*, 1997, 25: 692–698. [[Medline](#)] [[CrossRef](#)]
- 2) Walker PS, Erkman MJ: The role of the menisci in force transmission across the knee. *Clin Orthop Relat Res*, 1975, (109): 184–192. [[Medline](#)] [[CrossRef](#)]
- 3) Ciccotti MC, Kraeutler MJ, Austin LS, et al.: The prevalence of articular cartilage changes in the knee joint in patients undergoing arthroscopy for meniscal pathology. *Arthroscopy*, 2012, 28: 1437–1444. [[Medline](#)] [[CrossRef](#)]
- 4) Holmes R, Moschetti W, Martin B, et al.: Effect of evidence and changes in reimbursement on the rate of arthroscopy for osteoarthritis. *Am J Sports Med*, 2013, 41: 1039–1043. [[Medline](#)] [[CrossRef](#)]
- 5) Yoshimi T, Kikuchi T, Obara T, et al.: Effects of high-molecular-weight sodium hyaluronate on experimental osteoarthrosis induced by the resection of rabbit anterior cruciate ligament. *Clin Orthop Relat Res*, 1994, (298): 296–304. [[Medline](#)]
- 6) Schiavinato A, Finesso M, Cortivo R, et al.: Comparison of the effects of intra-articular injections of Hyaluronan and its chemically cross-linked derivative (Hylan G-F20) in normal rabbit knee joints. *Clin Exp Rheumatol*, 2002, 20: 445–454. [[Medline](#)]
- 7) Angele P, Johnstone B, Kujat R, et al.: Stem cell based tissue engineering for meniscus repair. *J Biomed Mater Res A*, 2008, 85: 445–455. [[Medline](#)] [[CrossRef](#)]
- 8) de Rezende MU, de Campos GC: Viscosupplementation. *Rev Bras Ortop*, 2015, 47: 160–164. [[Medline](#)] [[CrossRef](#)]
- 9) Bellamy N, Campbell J, Robinson V, et al.: Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*, 2006, (2): CD005321. [[Medline](#)]
- 10) Bannuru RR, Natov NS, Dasi UR, et al.: Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthritis Cartilage*, 2011, 19: 611–619. [[Medline](#)] [[CrossRef](#)]
- 11) Chevalier X, Jerosch J, Goupille P, et al.: Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis*, 2010, 69: 113–119. [[Medline](#)] [[CrossRef](#)]
- 12) Legré-Boyer V: Viscosupplementation: techniques, indications, results. *Orthop Traumatol Surg Res*, 2015, 101: S101–S108. [[Medline](#)] [[CrossRef](#)]
- 13) Colen S, van den Bekerom MP, Bellemans J, et al.: Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. *BMC Musculoskelet Disord*, 2010, 11: 264. [[Medline](#)] [[CrossRef](#)]
- 14) Fiorentini R: Proceedings of the United States Food and Drug Administration Advisory Panel on Orthopaedic and Rehabilitation Devices. Fairfax: CASET Associates 1996.
- 15) Mendoza G, Alvarez AI, Pulido MM, et al.: Inhibitory effects of different antioxidants on hyaluronan depolymerization. *Carbohydr Res*, 2007, 342: 96–102. [[Medline](#)] [[CrossRef](#)]
- 16) Goldenberg MM: Pharmaceutical approval update. *P&T*, 2014, 39: 337–344. [[Medline](#)]
- 17) Fakhari A, Phan Q, Thakkar SV, et al.: Hyaluronic acid nanoparticles titrate the viscoelastic properties of viscosupplements. *Langmuir*, 2013, 29: 5123–5131. [[Medline](#)] [[CrossRef](#)]
- 18) Bellamy N, Bell MJ, Goldsmith CH, et al.: Evaluation of WOMAC 20, 50, 70 response criteria in patients treated with hylan G-F 20 for knee osteoarthritis. *Ann Rheum Dis*, 2005, 64: 881–885. [[Medline](#)] [[CrossRef](#)]
- 19) Buma P, Ramrattan NN, van Tienen TG, et al.: Tissue engineering of the meniscus. *Biomaterials*, 2004, 25: 1523–1532. [[Medline](#)] [[CrossRef](#)]
- 20) Sweigart MA, Athanasiou KA: Toward tissue engineering of the knee meniscus. *Tissue Eng*, 2001, 7: 111–129. [[Medline](#)] [[CrossRef](#)]
- 21) Ahmed AM, Burke DL: In-vitro measurement of static pressure distribution in synovial joints—Part I: tibial surface of the knee. *J Biomech Eng*, 1983, 105: 216–225. [[Medline](#)] [[CrossRef](#)]
- 22) Moseley JB, O'Malley K, Petersen NJ, et al.: A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*, 2002, 347: 81–88. [[Medline](#)] [[CrossRef](#)]
- 23) Vermesan D, Prejbeanu R, Laitin S, et al.: Arthroscopic debridement compared to intra-articular steroids in treating degenerative medial meniscal tears. *Eur Rev Med Pharmacol Sci*, 2013, 17: 3192–3196. [[Medline](#)]

- 24) Fabricant PD, Rosenberger PH, Jokl P, et al.: Predictors of short-term recovery differ from those of long-term outcome after arthroscopic partial meniscectomy. *Arthroscopy*, 2008, 24: 769–778. [[Medline](#)] [[CrossRef](#)]
- 25) Miltner O, Schneider U, Siebert CH, et al.: Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—a prospective clinical trial. *Osteoarthritis Cartilage*, 2002, 10: 680–686. [[Medline](#)] [[CrossRef](#)]
- 26) 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. [[Medline](#)]
- 27) 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. [[Medline](#)] [[CrossRef](#)]
- 28) Kotevoglou N, Iyibozkurt PC, Hiz O, et al.: 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. [[Medline](#)] [[CrossRef](#)]
- 29) 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. [[Medline](#)] [[CrossRef](#)]
- 30) Wobig M, Bach G, Beks P, 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. [[Medline](#)] [[CrossRef](#)]