



Original Article

## Efficacy of single-dose hyaluronic acid products with two different structures in patients with early-stage knee osteoarthritis

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**Abstract.** [Purpose] There are many types of hyaluronic acid preparations, but no clear data are available about which preparations is more effective. The aim of this trial was to investigate the effectiveness of different types of hyaluronic acid preparations on pain and function of inpatients with knee osteoarthritis. [Subjects and Methods] All patients were diagnosed by clinical examination and x-ray. Ostenil PLUS<sup>®</sup> was injected into 28 patients (group 1, 1.6 million daltons), and MONOVISC<sup>®</sup> (group 2, 2.5 million daltons) was injected into 46 patients. Demographic data and Western Ontario and McMaster Universities Osteoarthritis Index and Visual Analog Scale scores were used for clinical evaluation at 1, 3, and 6 months post injection. [Results] In both groups, baseline Ontario and McMaster Universities Osteoarthritis Index and Visual Analog Scale scores were higher compared with those in subsequent evaluations. Based on the pre- and post-injection data, a significant reduction in all scores was observed after the injections for in both groups. According to intergroup comparisons, there was no significant difference in any of the scores between the two groups. [Conclusion] There were no difference in Ontario and McMaster Universities Osteoarthritis Index and Visual Analog Scale scores in patients with knee osteoarthritis injected with two different hyaluronic acid structures in short-term preparations.

**Key words:** Hyaluronic acid, Knee osteoarthritis, Single

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### INTRODUCTION

Osteoarthritis is one of the most common diseases around the world<sup>1)</sup>. It is more common among older patients and is of great importance in that it is associated with significant workforce loss among patients over 50 years of age. Osteoarthritis is a progressive disease causing important histological changes including degeneration of the cartilage as well as proliferation of bone, cartilage, and surrounding connective tissue, resulting in a severe functional limitations in patients<sup>2)</sup>.

Today, a number of different methods are used in the treatment of OA. Recent studies have shown that intra-articular hyaluronic acid (HA) injections are effective in controlling signs and symptoms of the disease<sup>3)</sup>. HA is a polysaccharide of

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the glycosaminoglycan family and is particularly essential for homeostasis of normal articulation. The concentration and molecular weight of HA in the synovial fluid are decreased in osteoarthritis<sup>4, 5</sup>).

HA administered via intra-articular injection may increase the regenerative effects of endogenous HA on joint cartilage and stimulate the synthesis of HA by synoviocytes, thus preventing the degradation of proteoglycans and collagen fibers in the extracellular matrix. HA stimulates the metabolism, prevents apoptosis of chondrocytes, exerts a moderate level of anti-inflammatory activity, reduces cytokine-induced enzyme production, and inhibits chondral degradation and articular inflammatory responses<sup>5, 6</sup>. After being injected, HA is taken up by specific joint receptors and exerts moderate anti-inflammatory action, reduces cytokine-induced enzyme production, and exhibits a direct analgesic effect by masking the joint nociceptors. HA injection both alleviates the symptoms and prevents the progression of joint degeneration<sup>4, 7</sup>). HA can be categorized into three groups based on molecular weight: low weight [between 0.5 and  $1 \times 10^6$  daltons (Da), each with 2–2.5 ml of HA, between 3 and 5 weekly applications], high weight ( $6 \times 10^6$  Da, single application of about 6 ml) and intermediate weight ( $2 \times 10^6$  Da)<sup>8</sup>). Preparations are reticulated with various adjuvant molecules (mannitol, sorbitol, chondroitin sulfate) to lengthen their duration of action. Clinical effects of different types of HA product and the superiority of one product over another have not been fully elucidated yet<sup>6</sup>).

There are many types of hyaluronic acid preparations (molecular weight, dosage, etc.), and there are no clear data about which preparations are more effective. In this trial, we aimed to investigate the effectiveness of different types of hyaluronic acid preparations on pain and function in patients with knee osteoarthritis.

## SUBJECTS AND METHODS

Between January 2013 and December 2013, data from patients with knee osteoarthritis, who were diagnosed recently by clinical examination and X-ray imaging, were evaluated retrospectively. A local ethics committee and health authority approved the study protocol (ID: KAEK/2014/2). Both written and oral consent were obtained from each participant. Identical case report forms were used to record data. The case report form included each participant's demographics, physical examination results, inclusion/exclusion criteria, medical history, and dated X-ray imaging. Data of patients who received injections but did not attend follow-up regularly were not included in the analysis. Standing plain radiographs were taken with the knees in an extended position. X-ray radiographs were evaluated for the presence of OA as defined by the Kellgren-Lawrence<sup>9</sup>).

**Patient selection, study design and HA preparations:** This study included patients with symptomatic early osteoarthritis of the knee, stable knees without malalignment, normal blood results, and normal coagulation profiles. The exclusion criteria included inflammatory joint diseases, previous intra-articular fracture of the knee, allergy to any substance related to the study medication, renal impairments, or metastatic tumors. All adverse effects, treatments given for them and outcomes were documented in each patient's medical records.

Patients who were enrolled in this study were dichotomized into two groups based on the type of injection administered (Ostenil PLUS<sup>®</sup> prefilled syringe, n=28, single dose; MONOVISC<sup>®</sup> prefilled syringe, n=46, single dose). Injections were performed with the patient in the supine position. The skin surrounding the injection site was sterilized. By gently pressing the patella medially, the lateral injection pathway was relieved. A 5 cc syringe with a 21-G needle was filled with 1 cc of lidocaine and 4 cc of normal saline. The entry was made from the lateral side of the patella. About 0.5 cc of the mixture was injected, and the needle was left in place for a few seconds to prevent backflow of the injected fluid. If the needle position was confirmed to be intra-articular, HA was injected. After injection, the joint was gently flexed and extended to ensure that the fluid was distributed throughout the joint space.

Ostenil PLUS<sup>®</sup> contains 2.0% of hyaluronate from fermentation and has a low molecular weight of 1.6 million Da. It is a high concentration HA, contains 10 mg of mannitol, and is available in 2 ml prefilled syringes. Mannitol acts as an antioxidant which helps to stabilize the chains of HA and extends the duration of action of HA inside the joint<sup>10–12</sup>).

MONOVISC<sup>®</sup> is a lightly cross-linked, high molecular weight hyaluronate (about 2.5 million Da). Each prefilled syringe contains 4 ml MONOVISC, which includes 22 mg/ml HA<sup>13, 14</sup>).

**Outcome measure(s):** The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a self-administered, disease-specific, health-related quality of life instrument that directs patients to answer questions concerning the knee or hip of interest. The WOMAC has a total score and scores for three subscales: pain, stiffness, and physical function. Higher scores indicate worse condition. For every question in the WOMAC, participants rate their pain, stiffness, or function using five ordinal responses: none, mild, moderate, severe, and extreme. Higher WOMAC scores indicated worse pain, stiffness, and functional limitations<sup>15</sup>). The Visual Analog Scale (VAS) measures a patient's pain intensity on a scale of 0 to 10. A score of 0 indicates no pain, whereas a score of 10 indicates the worst imaginable pain.

Descriptive data are presented as mean, standard deviation, median (lowest and highest), frequency, and percentage values. The Kolmogorov-Smirnov test was used to evaluate whether the data were distributed normally. Quantitative data were analyzed using the Mann-Whitney U test. The Wilcoxon test was used for the analysis of repeated measures. The  $\chi^2$  test was used for analysis of qualitative data, and Fisher's test was used when the chi-square test conditions were not met. Data analysis was performed using IBM SPSS Statistics 22.0.



## RESULTS

No significant differences were noted in age, gender, and occupation between the Ostenil PLUS and MONOVISC groups ( $p>0.05$ ) (Table 1). The grade of knee OA was significantly higher in the Ostenil PLUS group compared with in the MONOVISC group ( $p<0.05$ ) (Table 1).

There was no significant difference in VAS scores at 1, 3, and 6 months between the Ostenil PLUS and MONOVISC groups ( $p>0.05$ ). There was a significant decrease in VAS scores in both groups 1, 3 and 6 months compared with the baseline scores ( $p<0.05$ ) (Table 2). No significant differences were noted in WOMAC pain, stiffness, and physical function scores or WOMAC total scores at baseline or at 1, 3, and 6 months ( $p>0.05$ ) between the Ostenil PLUS and MONOVISC groups.

**Table 1.** Demographic distribution of patients

		Ostenil PLUS		MONOVISC	
Age (years)	Mean $\pm$ SD	60.2 $\pm$ 9.1		64.2 $\pm$ 8.1	
	Med (Min–Max)	59 (47–80)		64 (50–86)	
Gender (n, %)	Female	27	96%	46	100%
	Male	1	4%	0	0%
Occupation (n, %)	Housewife	27	96%	46	100%
	Retired	1	4%	0	0%
The grade of	II	16	57%	41	89%
	III	12	43%	5	11%

Mann-Whitney U test/ $\chi^2$  test (Fisher's test)

**Table 2.** Comparison of pre- and postinjection VAS and WOMAC scores of the groups

	Ostenil PLUS		MONOVISC	
	Mean $\pm$ SD	Median (min–max)	Mean $\pm$ SD	Median (min–max)
VAS				
Baseline	8.3 $\pm$ 0.5	8 (8–9)	8.1 $\pm$ 0.3	8 (8–9)
1 month	3.2 $\pm$ 2.3*	2 (2–8)	3.6 $\pm$ 2.5	2 (2–8)
3 months	3.2 $\pm$ 2.3*	2 (2–8)	3.6 $\pm$ 2.4	3 (2–8)
6 months	4.0 $\pm$ 1.8*	3 (3–8)	4.5 $\pm$ 2.1	4 (3–9)
WOMAC pain				
Baseline	20.0 $\pm$ 0.0	20 (20–20)	20.0 $\pm$ 0.0	20 (20–20)
1 month	11.5 $\pm$ 4.4*	10 (6–20)	12.0 $\pm$ 4.2	11 (7–20)
3 months	11.6 $\pm$ 4.1*	10 (5–20)	12.1 $\pm$ 4.1	10 (7–21)
6 months	13.2 $\pm$ 4.6*	10 (10–20)	13.0 $\pm$ 4.4	10 (10–20)
WOMAC stiffness				
Baseline	8.0 $\pm$ 0.0	8 (8–8)	8.0 $\pm$ 0.0	8 (8–8)
1 month	4.4 $\pm$ 1.9*	4 (2–8)	4.2 $\pm$ 2.2	4 (2–8)
3 months	4.6 $\pm$ 1.7*	4 (2–8)	4.8 $\pm$ 1.7	4 (2–9)
6 months	5.4 $\pm$ 1.8*	4 (4–8)	5.3 $\pm$ 1.8	4 (4–8)
WOMAC physical function				
Baseline	68.0 $\pm$ 0.0	68 (68–68)	66.3 $\pm$ 3.7	68 (57–68)
1 month	40.0 $\pm$ 13.9*	34 (19–68)	38.6 $\pm$ 15.6	34 (17–68)
3 months	38.5 $\pm$ 14.3*	34 (20–68)	40.8 $\pm$ 14.0	34 (19–68)
6 months	45.1 $\pm$ 15.4*	37 (34–68)	45.3 $\pm$ 14.4	38 (34–68)
WOMAC total				
Baseline	96.0 $\pm$ 0.0	96 (96–96)	94.3 $\pm$ 3.7	96 (85–96)
1 month	55.9 $\pm$ 19.9*	48 (31–96)	54.8 $\pm$ 21.8	49 (26–96)
3 months	54.8 $\pm$ 20.0*	48 (27–96)	57.7 $\pm$ 19.8	48 (28–97)
6 months	63.8 $\pm$ 21.7*	51 (48–96)	63.5 $\pm$ 20.5	55 (48–96)

Mann-Whitney U test/Wilcoxon test. \*Intragroup changes compared with the baseline  $p<0.01$



A significant decrease was found in WOMAC pain, stiffness, and physical function scores and WOMAC total scores at 1, 3, and 6 months compared with at in both groups ( $p < 0.05$ ), (Table 2).

## DISCUSSION

Intra-articular HA injection is commonly used in large joints for symptom relief in the treatment of OA<sup>16</sup>. Injections at the positions recommended by the ACR and OARSI are used as a secondary treatment for patients with knee osteoarthritis who are unresponsive to medical treatment. Acetaminophen and NSAIDs (nonsteroidal anti-inflammatory drugs) have been approved as the first-line therapy for knee osteoarthritis. On the other hand, there is evidence supporting the use of HA injections earlier in the treatment of early-stage OA. Previous studies reported that patients with lower grades of OA exhibited much better responses to HA injections compared with those with higher grades of OA. Patients who have received a diagnosis of OA within the previous year benefit more from HA injections. On the other hand, the rate of use of assistive devices is lower in patients who receive HA injections than in those who do not. Thus, it is beyond doubt that using HA at the earliest time possible after OA diagnosis can benefit patients<sup>17, 18</sup>. HA injections are at least as effective as NSAIDs, and are much safer than NSAIDs in terms of adverse effects. Furthermore, HA injections are associated with decreased need for NSAIDs and corticosteroids<sup>17, 18</sup>.

Today, clinical and biological effects of HA injection are still debated based on evidence-based medicine. A Cochrane review of 76 randomized controlled studies published in 2006 compared HA and other treatment modalities and concluded that HA injections had positive effects on pain, function, and global assessment, particularly in the 5–13 week post-injection period<sup>19</sup>. The American Academy of Orthopaedic Surgeons guidelines currently do recommend using HA injections for the treatment of symptomatic OA of the knee, suggesting that although meta-analyses of WOMAC pain and function subscale scores found positive effects, none of the improvements met the minimum clinically important thresholds<sup>20</sup>. The Osteoarthritis Research Society International guidelines currently do recommend the use of intra-articular HA injection for the treatment of osteoarthritis due to controversial results reported by relevant studies<sup>21</sup>. On the other hand, review of a number of studies, including two high-quality non-sponsored meta-analyses, demonstrated that HA injection was superior to steroids and a placebo in terms of efficacy and safety in the treatment of OA<sup>16</sup>. In the mentioned review, the effects of HA injection and physical therapy agents were compared in three studies, revealing that HA was as effective as TENS on disability and pain<sup>16</sup>. In three different studies comparing HA injection versus exercises for the treatment of knee osteoarthritis, no significant differences were noted in terms of long-term disability and pain between groups. The main problem in interpreting the results obtained from meta-analyses and studies is most likely that the studies used different HA preparations (low or high molecular weight, bacterial source, etc.). The success of HA injections depends on not only the molecular weight but also the dosage and frequency of use of HA. The results of four randomized placebo-controlled studies demonstrated that a total of three weekly intra-articular injections of HA for the treatment of knee OA was significantly more effective than a placebo in terms of pain (during rest and activities). During a 26-week follow-up period, it was found that patients receiving HA injections had significant symptom relief and needed less NSAIDs and steroids<sup>22–25</sup>.

The study presented here demonstrated that both single-dose HA preparations were effective in terms of pain and function. Improvements in VAS and all WOMAC scores were noted at 1 month postinjection and persisted at 3 and 6 months post injection in both groups. Comparison of the groups revealed no significant difference except for in the WOMAC stiffness score. The improvement in the WOMAC stiffness score achieved with Ostenil PLUS<sup>®</sup> was first noted at 1 month and persisted subsequently. The improvement in WOMAC stiffness score achieved with MONOVISC<sup>®</sup> was first noted at 1 month, but the improvement did not persist at 3 and 6 months. Accordingly, it can be concluded that patients in the Ostenil PLUS<sup>®</sup> group benefited more in terms of WOMAC stiffness score. Positive and significant results were obtained in both groups in this study. In terms of adverse effects, only two patients in the MONOVISC<sup>®</sup> group had swelling and redness of the joint within one week, but this, did not reach the level of statistical significance.

The main limitation of this study is that patients were permitted to use NSAIDs and other analgesics. On the other hand, patients were instructed to use one particular NSAID (diclofenac potassium) in order to achieve a homogeneous distribution. Both groups were requested to perform an exercise program to ensure that general treatment principles were followed. Because this study was a retrospective in nature, no comparison with a placebo was performed.

The results of the present study revealed no significant difference was noted in WOMAC and VAS scores between single-dose HA preparations; however, HA was found to be effective and should be used for the treatment of early stage-knee osteoarthritis.

### *Conflict of interests*

The authors declare that they have no conflict of interests.



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