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ORIGINAL ARTICLE

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Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment

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Abstract The aim of this study was to investigate the effects of intra-articular hyaluronic acid (HA) on symptoms, functional outcome, and changes in articular cartilage assessed by magnetic resonance imaging (MRI) in patients with knee osteoarthritis. Thirty patients were randomly assigned to treatment with HA (hylan G-F 20, Synvisc) or saline. The treatment group consisted of 20 patients receiving three weekly injections of HA into one or both knees (30 knees). The control group consisted of ten patients receiving three intra-articular injections of 2 ml saline at the same intervals (ten knees). To determine the effectiveness of the HA therapy, all patients were assessed prior to the injections (baseline) and after the 1st, 2nd, 3rd, and 8th weeks. Assessment comprised the following: pain at rest, at night, and on walking using a visual analogue scale (VAS); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and function scores; 15-m walking time; need for analgesics; and evaluation of treatment by the patients. MRI of patellofemoral (PF) articular cartilage was also examined before and after the course of injections at the 8th week. When compared to placebo, a significant statistical difference was found in all clinical parameters. On MRI, although the difference in the PF joint cartilage quality in the HA group before and after the treatment was statistically significant ($p < 0.05$), this significance was not detected between the groups after the treatment ($p > 0.05$). After the HA injections, a significant analgesic effect was seen as early as the 3rd week continuing up to the 8th week and functional improvement was seen at the 8th week. In conclusion, intra-articular injections of HA is an effective choice of treatment in patients with knee osteoarthritis.

Keywords Hyaluronic acid · Knee osteoarthritis · Magnetic resonance imaging

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Introduction

Osteoarthritis (OA) is the most common degenerative rheumatologic disease, resulting in significant morbidity and health care expense [1, 2]. The disease is characterized by several pathological events, including progressive erosion of the articular cartilage, synovial inflammation, and changes in the lubricating properties of synovial fluid [3, 4]. The loss of viscoelasticity of the synovial fluid in OA is the result of decrease in hyaluronic acid (HA), which is a major component of the synovial fluid and the major constituent of a 1- to 2-μm layer on the surface of articular cartilage [3, 5]. In OA, the decrease in the molecular weight and local amount of HA on the cartilage surface makes cartilage more susceptible to the mechanical stress [3].

Current treatment options for OA include use of nonpharmacologic modalities (patient education and physical and occupational therapy), pharmacologic agents (analgesics and nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections), and surgical treatment [1]. Although these medical interventions are successful to relieve the symptoms, they are not effective in retarding the progression of the disease. Thus, a new treatment modality that addresses both the underlying etiology of OA and delaying its progression has been highly desired [5, 6]. Intra-articular HA injection known as viscosupplementation has been developed in this respect which replaces and supplements synovial fluid in patients with OA [5, 7]. The effectiveness of HA has been shown by in vitro and clinical studies [4, 8, 9].

Although there are clinical studies showing improvement primarily in pain complaints, we have not met any study in the literature determining the extent of articular cartilage change after treatment with HA. To our knowledge, this is the first study investigating the articular cartilage change after viscosupplementation which can be detected by magnetic resonance imaging (MRI).

The objective of the study was to assess the effects of intra-articular injections of hylan G-F 20 (Synvisc) on symptoms and functional outcome of knee OA and to investigate whether a qualitative change occurs in knee cartilage using MRI.

Material and methods

In this prospective, randomized, and placebo-controlled clinical trial, HA or saline was injected intra-articularly in 30 patients with clinical and radiological signs of osteoarthritis of the knee joint. The demographic data of the study and control subjects are presented in Table 1. Patients matching the criteria of the American College of Rheumatology for knee OA with radiological evidence and symptoms were included in the study [10]. Knee pain persisting for more than 1 year and pain over 40/100 according to the visual analogue scale (VAS) for more than 15 days in the last month were the inclusion criteria of the study. Patients were excluded if they had any other serious systemic diseases, depression, avian allergy, other arthropathies, neoplasms, recent trauma, knee instability, effusion in the knee, a varus or valgus deformity of $>15°$, or flexion contracture of $>20°$, and had received intra-articular corticosteroids within the 6 months prior to the start of the study.

Anteroposterior and lateral knee radiographs while standing were obtained at the beginning of the study. They were radiologically graded according to the Kellgren–Lawrence Index [11]. MR images of the knee were acquired using a knee coil in a 0.5 T superconductive magnet (MR Max, General Electrics, Milwaukee, Wis., USA). Prior to the first injection and at the 8th week following the injection, T1-weighted gradient echo images in sagittal, coronal, and transverse planes and T2-weighted and proton density-weighted sagittal and transverse images were obtained followed by T1-weighted images after the injection of intravenous gadolinium (0.1 mmol/kg, Magnevist, Schering, Berlin, Germany). MR images were reported by a consultant radiologist (NK). Patients were evaluated and graded according to meniscal abnormalities, ligamentous changes, subchondral cysts, subchondral sclerosis, osteophytes, Baker's cyst, and knee effusion prior to the injections [12].

Table 1 Demographic characteristics of the patients

Variable	HA group $n=30$	Saline group $n=10$	p value
Age (years)	52.6 ± 7.16	57.6 ± 2.77	>0.05
Gender, number of subjects			>0.05
Male	6		
Female	14	10	
Height	161.20 ± 6.09	163.90 ± 5.62	>0.05
Weight	74.43 ± 11.39	71.90 ± 10.22	>0.05
Symptom duration (years)	2.70 ± 0.81	1.80 ± 0.63	>0.05
Kellgren–Lawrence grade	1.86 ± 0.81	1.80 ± 0.63	>0.05

Pre-treatment and post-treatment patellofemoral articular cartilage changes were staged according to a modified Shahriaree classification: grade 0 normal cartilage, grade 1 cartilage softening and focal hypointensity, grade 2 mild surface fibrillation and/or less than 50% loss of cartilage thickness, grade 3 severe surface fibrillation and/or loss of more than 50% of cartilage thickness but without exposure of subchondral bone, and grade 4 complete loss of cartilage with subchondral bone exposure [13].

Thirty patients were randomly assigned to treatment with HA or placebo. The treatment group consisted of 20 patients receiving three weekly intra-articular injections of HA into one or both (if bilaterally symptomatic) of the knees (total of 30 knees). The control group consisted of ten patients receiving three intra-articular injections of 2 ml saline at weekly intervals (total of ten knees).

After completing the pretreatment survey, 2 ml of intra-articular hylan G-F 20 solution (10 mg/ml Synvisc) or placebo (2 ml saline) were injected under sterile conditions using a medial approach by a physician. After injections, knees were wrapped up with bandage and the patients were instructed to rest for 24 h. Additional physiotherapy or anti-inflammatory drugs were not applied. Paracetamol was permitted for analgesia.

Patients were evaluated according to the parameters shown below prior to the injections and at post-treatment weeks 1, 2, 3, and 8.

1. Pain at rest, at night, and on walking was evaluated by a 100-mm VAS.
2. All individual [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): pain by WOMAC-A, stiffness by WOMAC-B, functional impairment by WOMAC-C] responses were graded using a 5-point Likert scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = extreme). The possible range for the summed WOMAC pain score is 5–25, whereas the possible ranges for the stiffness and function scores are 2–10 and 17–85, respectively [14].
3. Walking time for 15 m and need for paracetamol were noted.
4. The evaluation of treatment by the patient (1 = treatment is not effective, 2 = less effective, 3 = effective, 4 = very effective) was assessed.

Wilcoxon's rank sum test was used for comparison of the variables before and after treatment and the Mann–Whitney U test was used for comparison of the HA and saline groups. The Bonferroni correction was applied for

multiple testing. For this purpose we multiplied all p values by 9 (number of clinical parameters). After this correction, p values less than 0.05 were considered to be statistically significant.

Results

All patients completed the trial. There were no statistically significant differences in age, gender, weight, height, and Kellgren–Lawrence radiologic grading between groups ($p > 0.05$). Table 1 shows the main demographic data.

There were no statistically significant differences in all pain parameters and paracetamol use between the two groups before the study ($p > 0.05$). The comparison of the two groups and the baseline values are shown in Table 2.

There were no statistically significant differences between groups in WOMAC-A, WOMAC-B, WOMAC-C, and 15-m walking time before the study ($p > 0.05$). After the treatment, WOMAC parameters, 15-m walking time, and evaluation of treatment by the patients were statistically changed compared to baseline in the HA group. In the saline group, these parameters showed no differences. There were also statistically significant differences between the two groups in all of these parameters except WOMAC-B and 15-m walking time as shown in Table 3.

Figure 1 shows the mean VAS scores assigned by the evaluator during the 8-week study period. Rest pain decreased starting from the 3rd week and continuing to the 8th week (Table 2). Night pain, pain on walking, and need for paracetamol in the HA group were significantly lower than in the saline group at the 8th week.

Figure 2 displays the mean WOMAC pain, stiffness, and physical function scores at each time point during the study. The patients in the HA group had a greater reduction in the WOMAC pain score beginning in the 3rd week and the improvement continued through week 8 ($p < 0.05$) compared to the placebo group. The difference between the groups in WOMAC-C functional impairment score was statistically significant at week 8.

There were no statistically significant differences in MRI findings of meniscal abnormalities, ligamentous changes, subchondral cysts, subchondral sclerosis, osteophytes, Baker's cyst, and joint effusion between the two groups before the study ($p > 0.05$). Before and after the treatment, there was no significant change in patellofemoral articular cartilage in the saline group ($p > 0.05$), but statistically significant improvement was found in the HA group ($p < 0.05$). However, there was no statistically significant difference between the groups ($p > 0.05$) after the treatment. Pretreatment and posttreatment Shahriaree grades are shown in Table 4.

Discussion

In OA, the reduced molecular weight and concentration of hyaluronan results in low viscosity of the synovial fluid and an increase in cartilage loading. This loss of elastoviscosity decreases the lubrication and protection of the joint tissues. As HA may prevent the damage of articular cartilage and secondarily protects the subchondral bone from excessive stress, the loss of lubrication causes increased stress forces, which further disrupt the collagen network that is essential to the integrity of the articular surface [5, 15].

Hyaluronate viscosupplementation was suggested as a treatment for knee OA. Although the mechanisms of action still remain unclear, inhibition of inflammatory mediators, stimulation of cartilage matrix synthesis and inhibition of cartilage degradation, and a direct protec-

Table 2 VAS parameters and need for paracetamol at baseline and 1st, 2nd, 3rd, and 8th weeks

	HA group (mean ± SEM)	Saline group (mean ± SEM)	HA vs saline (p value)[b]
VAS night—baseline	45.00 ± 2.82	54.0 ± 3.71	> 0.05
1st week	40.00 ± 2.58[a]	46.0 ± 4.76	> 0.05
2nd week	32.33 ± 2.38[a]	39.0 ± 3.14	> 0.05
3rd week	27.33 ± 1.72[a]	37.0 ± 3.00	> 0.05
8th week	22.66 ± 2.08[a]	44.0 ± 3.26	< 0.05
VAS rest—baseline	46.66 ± 1.99	51.0 ± 2.33	> 0.05
1st week	44.33 ± 2.18	45.0 ± 3.07	> 0.05
2nd week	35.33 ± 2.28[a]	42.0 ± 2.00	> 0.05
3rd week	29.00 ± 1.75[a]	39.0 ± 1.79	< 0.05
8th week	22.33 ± 1.56[a]	41.0 ± 1.79	< 0.05
VAS walking—baseline	71.0 ± 1.20	67 ± 2.13	> 0.05
1st week	64.66 ± 1.64[a]	58.0 ± 3.26	> 0.05
2nd week	52.66 ± 2.08[a]	54.0 ± 3.05	> 0.05
3rd week	46.66 ± 2.16[a]	50.8 ± 1.81[a]	> 0.05
8th week	40.0 ± 2.03[a]	53.8 ± 2.25	< 0.05
Need for paracetamol—baseline	1.0 ± 0.00	0.9 ± 0.13	> 0.05
1st week	0.3 ± 0.00[a]	0.4 ± 0.16	> 0.05
2nd week	0.0 ± 0.00[a]	0.0 ± 0.00[a]	> 0.05
3rd week	0.0 ± 0.00[a]	0.1 ± 0.16[a]	> 0.05
8th week	0.0 ± 0.00[a]	0.7 ± 0.15	< 0.05

[a]Comparison with the baseline values ($p < 0.05$)
[b]Comparison of the two groups

Table 3 Parameters for WOMAC, 15–m walking time, and evaluation of treatment by the patients at baseline and after weeks 1, 2, 3, and 8

	HA group (mean ± SEM)	Saline group (mean ± SEM)	HA vs saline (p value)[b]
WOMAC-A—baseline	15.72 ± 0.47	17.6 ± 0.45	> 0.05
1st week	14.81 ± 0.54[a]	16.9 ± 0.85	> 0.05
2nd week	13.23 ± 0.44[a]	15.3 ± 0.61	> 0.05
3rd week	11.40 ± 0.41[a]	14.1 ± 0.48	< 0.05
8th week	9.36 ± 0.34[a]	14.6 ± 0.56	< 0.05
WOMAC-B—baseline	6.33 ± 0.23	6.1 ± 0.52	> 0.05
1st week	6.06 ± 0.24	5.9 ± 0.56	> 0.05
2nd week	4.86 ± 0.22[a]	5.5 ± 0.54	> 0.05
3rd week	4.20 ± 0.23[a]	5.0 ± 0.36	> 0.05
8th week	3.50 ± 0.24 [a]	5.1 ± 0.48	> 0.05
WOMAC-C—baseline	49.63 ± 1.68	47.8 ± 1.46	> 0.05
1st week	48.73 ± 0.93	47.7 ± 1.62	> 0.05
2nd week	44.06 ± 0.85	47.1 ± 1.68	> 0.05
3rd week	40.90 ± 1.11[a]	46.5 ± 1.62	> 0.05
8th week	35.90 ± 1.04[a]	47.4 ± 1.68	< 0.05
15-m walking time—baseline	21.03 ± 0.84	18.0 ± 0.71	> 0.05
1st week	20.56 ± 0.80	17.9 ± 0.75	> 0.05
2nd week	18.73 ± 0.80[a]	17.1 ± 0.60	> 0.05
3rd week	17.40 ± 0.53[a]	16.6 ± 0.49	> 0.05
8th week	16.13 ± 0.55[a]	17.0 ± 0.64	> 0.05
Evaluation of treatment by the patient			
1st week	1.7 ± 0.13	1.8 ± 0.24	> 0.05
2nd week	2.3 ± 0.13[a]	2.0 ± 0.21	> 0.05
3rd week	2.6 ± 0.11[a]	2,3 ± 0,21	> 0.05
8th week	3.6 ± 0.12[a]	1.8 ± 0.13	< 0.05

[a]Comparison with the baseline values ($p < 0.05$)
[b]Comparison of the two groups

tive action on nociceptive nerve endings are some of the proposed mechanisms [16]. Hylan G-F 20 is a cross-linked form of purified hyaluronan with extremely high molecular weight, elastoviscous fluid with rheologic properties similar to the young healthy human synovial fluid in the knee joint [4, 5, 9]. We investigated the effects of intra-articular injections of hylan G-F 20 (Synvisc) on pain, stiffness, and function and knee cartilage quality as detected by MRI in patients with knee OA.

In this study, significant improvement was observed in pain at rest and the WOMAC-A pain subscale starting from the 3rd week, and this improvement was maintained until the end of the 2-month follow-up period in the HA group. Also a significant decrease was observed in walking and night pain at the 8th week. In clinical trials, intra-articular hyaluronan preparations showed clinically significant pain relief in comparison to that reported after intra-articular injection of a placebo [17–20]. Grecomoro et al. [17] reported statistically significant differences in favor of the HA group for spontaneous pain, pain under load, pain on touch, and pain on walking as early as the end of the 1st week. This effect persisted during the 2-month follow-up period. In the study by Wobig et al. [18], similar findings were observed from the 3rd week in the HA group and were maintained until the end of the 3rd month of the follow-up period. Lussier and Naimiki reported a decrease in pain in the early period of the treatment and in patients with early

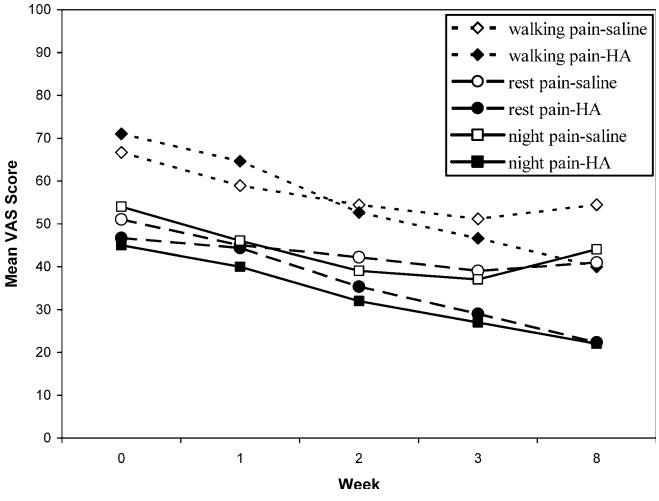

Fig. 1 Pain assessment for 8-week follow-up period using a 100-mm VAS

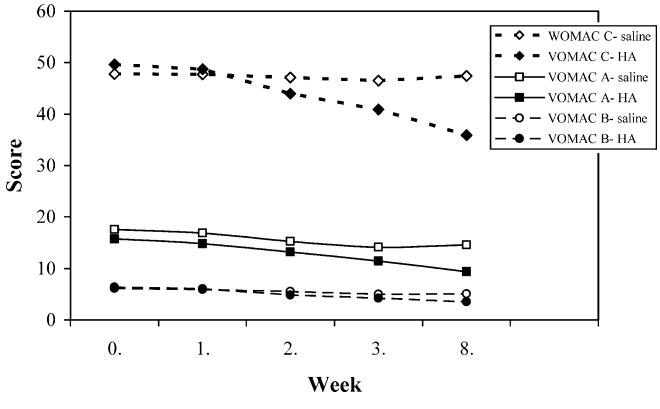

Fig. 2 Mean change from baseline in pain score (WOMAC-A), stiffness score (WOMAC-B), and functional impairment score (WOMAC-C) of groups for 8 weeks follow-up. *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Table 4 Changes in Shahriaree grades of the groups

Shahriaree classification	HA group (*n*)	Saline group (*n*)	*p**
Baseline			
0	1	2	> 0.05
1	12	4	
2	13	4	
3	3	0	
After 8 weeks			
0	1	2	> 0.05
1	16	4	
2	11	3	
3	1	1	
*p***	< 0.05	> 0.05	

*Comparison of the two groups
**Comparison with the baseline

radiological grade and without excessive effusion [19, 20]. In our study, no patient showed grade IV according to Kellgren and Lawrence. Also, the need for paracetamol in the HA group was significantly lower than in the saline group at the 8th week. The results of this study confirm that HA has an analgesic effect in the early period and modulates pain perception in patients with knee OA.

In their series, Carabba et al. [21] reported better improvement in stiffness at the 5th week up to the 8th week with HA compared to orgotein. In three trials evaluating HA and corticosteroid use, a reduction in stiffness was detected at the early and late periods with HA [22–24]. In our study, the difference between the groups in WOMAC-B stiffness scores was not statistically significant during the study.

The difference in WOMAC-C physical function scores between the groups was statistically significant at week 8. This result reflects that the relief of the knee symptoms provides considerable improvement in activities of daily living.

There were no statistically significant differences in 15-m walking time between the groups. Adams et al. [25] had observed an improvement in 15-m walking time in the 12th week. Kolarz et al. [26] reported 50% increases in walking distance at the 5th week. Carrabba et al. [27] detected 60% increases in the maximum duration of walking.

In this study via requesting the patients' evaluation of the treatment, there was a statistically significant difference between groups at the 8th week. In a study of Kolarz et al. [26] requesting the evaluation of effectiveness of the treatment on the 35th day, 55.5% of the patients in the HA group appraised it to be "good" or "very good."

In our study, no systemic adverse effects was seen and none of our patients dropped out of the treatment program. Only one patient complained of mild transient local pain in the injection area a day after the first injection. In other studies, undesirable events occurring after injections were mostly inconsiderable and transient [19].

Creamer et al. [28] in their placebo-controlled study administered five weekly HA injections to 23 patients with bilateral knee osteoarthritis. Synovial fluid volume analysis was made by MRI before and 6 weeks after the first injection. They did not detect any change in the pre- and post-MR images. As they mentioned it would be better if the follow-up period were longer. In our study, we evaluated the structural quality of the cartilage instead of the synovial fluid volume, which is an important criterion for the evaluation of OA progression. Progressive cartilage loss, a hallmark of OA, is identified on X-rays by joint space narrowing, an indirect measurement of cartilage thinning. Radiographic evidence of joint space loss, however, occurs late in the disease process after a significant portion of cartilage has been lost. MRI, with superior soft tissue imaging capabilities, may measure cartilage loss directly by using planar or volumetric techniques. We used intravenous gadolinium because it has been shown to be effective in the early detection of the cartilage degeneration before external structural changes occur and in identification of small (2 mm) full-thickness lesions on T1-weighted images [29]. In the literature, no study has addressed the impact of therapy on the cartilage. Thus, our study represents the first in this respect. MRI can provide direct visualization of the hyaline cartilage and has the potential to provide accurate quantification with sensitivity to degenerative changes [30]. In this study, on the MR images taken after 8 weeks from the first injection, a statistically significant difference in the PF joint cartilage in the HA group was detected, whereas it was not significant compared to the control group. There is the probability that 8 weeks time may not be enough to investigate the degeneration process of cartilage structure.

There are limitations in our study. The small number of patients in our study may not be enough to draw strong conclusions on the clinical and qualitative effects of intra-articular HA injections on the articular cartilage. Another important drawback of this study is that the conventional MRI sequences we used in the evaluation of cartilage quality are limited in providing a detailed assessment of cartilage, lacking spatial and contrast resolution. Fat-suppressed 3D spoiled GRE (3D SPGR) or 3D double echo in the steady state (DESS) imaging would have been more sensitive than standard MRI for detection of hyaline cartilage defects in the knee, producing high contrast resolution between cartilage and fluid and reducing the effects of chemical shift and partial volume artifacts [2931,]. However, these state-of-the-art MRI techniques are not currently available in our MR scanner.

In conclusion, intra-articular injection of hylan G-F 20 is an effective choice of treatment in patients with knee osteoarthritis relieving the clinical symptoms, and possibly improving the quality of the articular cartilage. Multicenter studies using current state-of-the-art MRI techniques in cartilage imaging with larger patient groups and longer observation periods are warranted to

determine the reproducibility of our results and the effect of HA on the quality of articular cartilage.

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