

# Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up

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## Abstract

### Objectives

*To compare the long-term effects of high and low molecular weight hyaluronic acid (HA) applications in severe (Kellgren Lawrence stage III) osteoarthritis (OA) of the knee.*

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### Methods

*In a prospective clinical trial 184 knees (92 patients) with radiographic Kellgren Lawrence stage III OA were randomized to receive either 3 intra-articular high molecular weight HA (Hylan G-F 20) injections or 3 low molecular weight HA (Orthovisc) injections at one-week intervals. Patients were evaluated by the Hospital for Special Surgery (HSS) Knee Score and were followed-up for 12 months.*

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### Results

*The total HSS score in high molecular weight HA patients improved from  $71.8 \pm 11.6$  to  $86.7 \pm 11.6$  and in low molecular weight HA patients from  $66.7 \pm 11.0$  to  $86.6 \pm 9.1$  at the end of the trial ( $p < 0.01$ ). There were no statistically significant differences between the groups and both had improved in all parameters at the latest follow-up ( $p = 0.000$ ).*

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### Conclusions

*Three intra-articular injections at intervals of 1 week of both HA preparations resulted in a pronounced reduction in pain and improved function as measured by the HSS score during a period of 52 weeks, without complications.*

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### Key words

Advanced osteoarthritis, knee, high molecular weight hyaluronic acid, low molecular weight hyaluronic acid.

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## Introduction

Hyaluronic acid (HA) is a major component of the extracellular matrix of cartilage and the superficial layers of the synovial membrane and is present in high concentrations in the synovial fluid (1). In osteoarthritis (OA) there is a reduction in the elastoviscosity of the synovial fluid secondary to a decrease in the molecular weight and concentration of HA (2). A number of controlled studies have documented the therapeutic value of intra-articular applications of HA (1, 3-16). Several HA preparations are currently available, in two categories: low (0.5–2 mDa) and high (6–7 mDa) molecular weight HA (2, 17). According to some authors higher molecular weight HA is more effective than lowers molecular weight HA (1, 5, 7, 13, 18). However, others found no difference in the efficacy between the low and high molecular weight HA preparations (6, 19). Review of the literature revealed only four studies comparing high and low molecular weight HA (20-23), but the grade of OA was not uniform in these series. Since HA applications have proven to be an effective treatment for moderate to severe OA of the knee (24-26), we conducted the present study in order to evaluate the effects of high and low molecular weight HA in severe (Kellgren Lawrence stage III) OA of the knee with long-term follow-up.

## Materials and methods

The series consisted of 92 patients (184 knees) with primary OA of the knee as defined by the American College of Rheumatology criteria (27), and all were seeking treatment. All patients had Kellgren Lawrence stage III OA with narrowing of the joint space and sclerosis of the subchondral bone (28). Any patient with radiographic appearance of pseudocysts was defined as having Kellgren Lawrence grade IV OA and excluded from the study. All radiographs (AP, Lateral, and Merchant) were evaluated by two orthopaedic surgeons and if consensus was not achieved, then the patient was not included in the study.

All patients underwent a full medical examination and details of medication

during the last year were recorded. Patients receiving non-steroidal anti-inflammatory drugs were asked to discontinue them for the duration of the study, beginning from 15 days prior to the study. If not possible due to the presence of other diseases, then the patients were excluded from study.

Exclusion criteria included: previous fracture around the knee, joint effusion, inflammatory arthritis, previous intra-articular injections or any other invasive procedure in the knee, significant comorbidity (renal, hepatic or heart disease), and chicken or egg allergy.

After the written informed consent of the patients was received, all patients with bilateral knee involvement were given a number and using a computer program (Excel 2000), 46 of them were randomly assigned to receive low molecular weight HA (group L) and 46 of them to receive high molecular weight hylan (group H).

Prior to the treatment, the knee function of all patients was evaluated using the Hospital for Special Surgery (HSS) Knee Score criteria, which is based on a total of 100 points. The score is divided in to seven categories: pain, function, range of motion, muscle strength, flexion deformity, instability and subtractions. Scores between 100 and 85 points are considered excellent results; scores between 84 and 70 points are good results; scores 69 and 60 points are fair, and scores less than 60 are considered poor results (29).

Both groups received three injections of HA [low-molecular weight HA (molecular weight 1.55 mDa), Orthovisc®, Anika, Biomeks, Turkey and high-molecular weight hylan; cross-linked HA (molecular weight 6 mDa), Synvisc®, Hylan G-F 20, Wyeth, Turkey] separated by 1-week intervals. In all cases, both knees were injected.

All patients in both groups were evaluated at 1, 2, 3, 6 weeks and at 3, 6, 12 months by means of the HSS score. The physician administered the injections and an independent physical therapist (not involved in the therapy) assessed the efficacy and safety in the same patient. In this way, neither the patient nor the physical therapist was aware of the nature of the treatment.

The patient and physician (or physical therapist) who was responsible for the evaluation of the patient remained blinded throughout the entire study.

### Intent-to-treat analyses

The results of treatment were assessed during each patient visit. All patients who received at least one intra-articular HA injection were included in the intent to treat analyses. In addition to the analyses of the intent to treat population, analyses were done on patients who completed the study, had no major protocol violations. Change from baseline within treatment groups was assessed using Wilcoxon's signed ranks test, where as between treatment group differences were assessed using Mann Whitney-U tests. Chi-square tests were used to analyses categorical variables. Analysis of variance with repeated measures was applied to the efficacy data from the beginning of the study to 12 months of follow-up. A p value of < 0.05 was considered significant. All data analysis was performed by using SPSS for Windows, version 10.0.

## Results

### Intent-to-treat population

The 92 patients constituted the intent to treat population. The demographic data and the baseline disease characteristics at the start of the study are displayed in Table I. There was no statistically significant difference in demographic data or clinical parameters, except walking distance, used in the study.

### Discontinuation of treatment

In the intent to treat population, 30 patients in group L (63.7 %) and 32 patients in group H (69.5 %) completed the 12 months study. Progress of patients was displayed in Figure 1. The causes of discontinuation are displayed in Table II.

### Effectiveness population

The effectiveness population consisted of 62 patients (30 patients in group L and 32 patients in group H) who completed the 12 months study without major violations. The demographic data and the baseline disease characteristics at the start of the study are displayed in

**Table I.** Baseline characteristics of the 92 patients with osteoarthritis studied, expressed as the mean (SD).

Characteristics	Intent to treat population			Effectiveness population		
	Group H (n = 46)	Group L (n = 46)	P value	Group H (n = 32)	Group L (n = 30)	P value
Age (years)	60.5 (9.5)	60.6 (9.6)	0.96	60.9 (9.5)	60.8 (9.3)	0.95
Sex (men/ women)	8/38	9/37	0.70	7/25	7/23	0.08
Body mass index (kg/m <sup>2</sup> )	30.7 (4.9)	29.6 (4.4)	0.10	29.9 (5.0)	29.2 (4.7)	0.87
Pain at activity*	5.2 (4.7)	4.4 (4.2)	0.23	6.0 (5.1)	4.3 (4.4)	0.06
Pain at rest*	8.1 (5.0)	9.1 (4.5)	0.21	8.8 (4.6)	9.4 (5.2)	0.36
Pain during climbing stairs*	2.1 (0.6)	2.1 (0.7)	0.51	2.2 (0.8)	2.1 (0.8)	0.41
Pain during transfer activities*	2.6 (1.2)	2.5 (1.1)	0.81	2.7 (1.3)	2.4 (1.0)	0.06
Walking distance*	8.3 (3.3)	5.4 (3.6)	0.00	8.4 (3.2)	5.1 (3.5)	0.00
Range of motion (degrees)	114.4 (9.2)	113.0 (10.0)	0.12	115.5 (7.4)	115.6 (8.7)	0.94
Total HSS** score	70.1 (11.7)	67.7 (10.3)	0.10	71.8 (11.6)	66.7 (11.0)	0.02

\* Graded by the HSS score; \*\* Hospital for Special Surgery.

Table I. Prior to treatment patients in group H had more total HSS score (p = 0.02) and could walk more than the patients in group L (p = 0.000). This difference in walking distance persisted up to three weeks but patients in group L had less pain at rest at 6 weeks (p = 0.01) and less pain at activity at three months (p = 0.03). However, there was no difference between the groups at six and twelve months (Table III). Both groups improved in all parameters at the latest follow-up (p = 0.000).

Throughout the study no complications due to HA injection, such as pain, effusion, synovitis, haemarthrosis or septic arthritis were recorded.

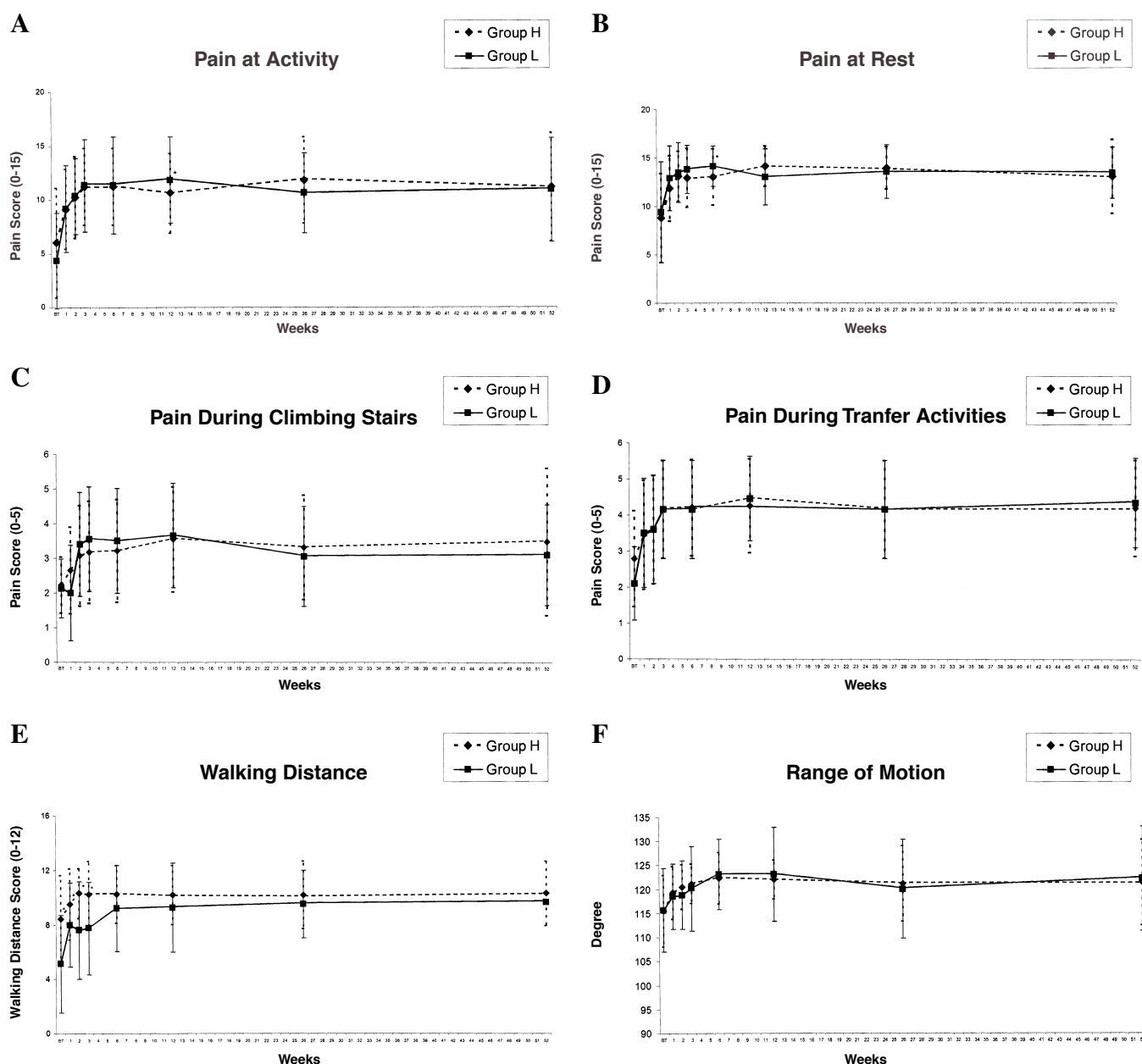
## Discussion

Although the pathogenesis of OA has been elucidated in great detail, at present no definitive treatment exists for the majority of patients suffering from this debilitating disease (5). The safety and efficacy of several HA formulations have been investigated in patients with OA of the knee (1, 3, 6, 9, 10, 12, 14-16). However, there are conflicting results about radiographic stages on treatment outcomes (1, 5-7, 13, 18, 19). Some studies suggest that HA therapy is not effective in cases of advanced OA, especially when architectural changes have already taken place (1, 5, 7, 13, 18). However, according to Neustadt (24), Waddell *et al.* (25), and Wen (26) HA application is effective in mo-

derate to severe OA of the knee. Our results are in accordance with Neustadt (24), Waddell *et al.* (25) and Wen (26), in that 67.3% of our patients with Kellgren Lawrence Stage III improved at one year of follow-up (Fig. 2). This point is especially important in that these patients were candidates for total knee replacement (TKR) surgery and our intervention either using high and low molecular weight HA allowed us to postpone the surgery.

There are four studies in the literature (20-23) comparing the effects of high and low molecular weight HA, but it is difficult to compare our results with them. First of all, some series included patients with different stages of OA (20-22) or else the staging was not clear (23). The period of follow-up was 3 months in the studies of Wobig *et al.* (20) and Bayramoglu *et al.* (23) and 6 months in Roman *et al.* (21). Also, Roman *et al.* (21) and Bayramoglu *et al.* (23) had not powered their studies for an intent-to treat analysis, but used only a "completers" analysis. That these were not an intent-to treat analyses becomes important when trying to make comparisons, particularly between different HA preparations. Additionally, the studies of Roman *et al.* (21) and Bayramoglu *et al.* (23) were not blinded and the number of patients included was less than 50.

Although several complications were reported due to HA injections (2, 5, 6,



**Fig. 1.** Comparison of both groups throughout the study.

- A. Pain at activity (\* $p < 0.05$ )  
 B. Pain at rest (\* $p < 0.05$ )  
 C. Pain during climbing stairs  
 D. Pain during transfer activities  
 E. Walking distance (\* $p < 0.05$ )  
 F. Range of motion (degrees)

**Table II.** Details of the patients excluded from the study.

Reason for exclusion	Group H (pt. no.)	Group L (pt. no.)
Lost to follow-up	3	4
Due to lack of efficacy	4	5
Free from pain	3	3
Prosthesis	2	4
Second injection cure	2	-
Total	14	16

8, 13, 14, 19-22, 30), we observed no complications, either minor or major, in the two HA groups. It is essential to bear in mind the importance of full aspiration of any synovial fluid that is present and meticulous attention to needle placement in order to optimize efficacy and minimize adverse effects (31).

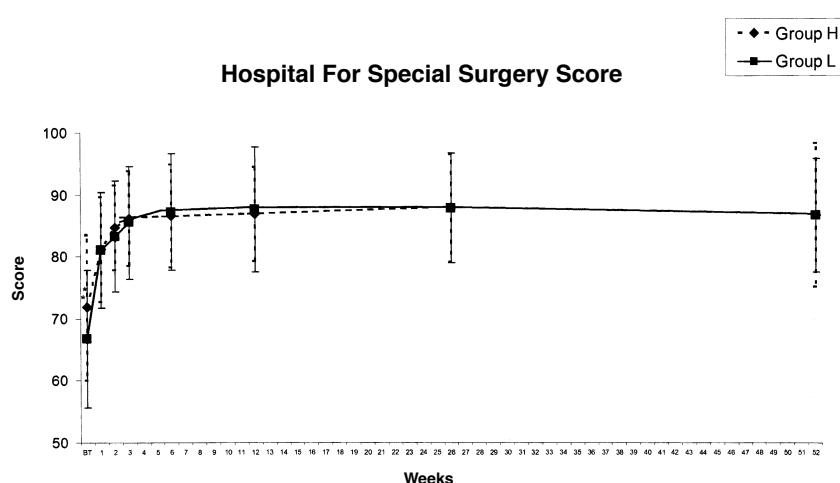
On the basis of this prospective, ran-

**Table III.** Mean improvement from baseline (effectiveness populations).

	Group	1 week	2 week	3 week	6 week	3 months	6 months	12 months
Pain at activity	Group H	3.3	4.2	5.2	5.2	4.6	5.3	5.1
	Group L	4.8	6.0	7.0	7.0	7.5*	7.0	6.5
Pain at rest	Group H	3.0	4.3	4.1	4.2	4.6	5.1	4.3
	Group L	3.5	4.0	4.4	4.7*	4.0	4.1	4.0
Pain while climbing stairs	Group H	0.4	0.8	0.9	0.9	1.3	1.0	1.2
	Group L	0.7	1.2	1.4	1.3	1.5	0.9	0.9
Pain during transfer activities	Group H	0.6	0.8	1.3	1.4	1.4	1.3	1.4
	Group L	1.1	1.2	1.7	1.7	2.0	1.7	1.9
Walking distance	Group H	1.0	1.8	1.8	1.8	1.7	1.7	1.8
	Group L	2.8*	2.4*	2.6*	4.0	4.1	4.4	4.5
Range of motion (degrees)	Group H	3.7	4.9	5.6	6.8	6.4	5.5	5.8
	Group L	2.8	3.1	4.5	7.4	7.4	4.3	6.4
Total HSS** score	Group H	9.3	12.9	14.4	14.7	15.0	16.0	14.9
	Group L	14.2	16.5	18.7	20.4	20.8	21.0	19.9

\* Indicates statistically significant improvement as compared to the other group.

\*\* Hospital for Special Surgery.

**Fig. 2.** Mean Hospital for Special Surgery Score.

domized, double-blind study of patients with more advanced knee OA (stage III), we conclude that three intra-articular injections at intervals of one week of either HA preparation produced a marked reduction in pain and improved function by the HSS score during a period of 52 weeks, without complications. The data presented suggests that both HA preparations may present well tolerated alternatives to non-steroidal anti-inflammatory drugs or the intra-articular injection of corticosteroids.

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