

Comparison between High and Low Molecular Weight Hyaluronates in Knee Osteoarthritis Patients: Open-label, Randomized, Multicentre Clinical Trial

PB LEE¹, YC KIM¹, YJ LIM¹, CJ LEE¹, WS SIM², CW HA³, SI BIN⁴, KB LIM⁵,
SS CHOI⁶ AND SC LEE¹

¹Department of Anaesthesiology and Pain Medicine, Seoul National University College of Medicine; ²Department of Anaesthesiology and Pain Medicine and ³Department of Orthopaedic Surgery, SungKyunKwan University College of Medicine; ⁴Department of Orthopaedic Surgery, Ulsan University College of Medicine; ⁵Department of Rehabilitation Medicine, Inje University College of Medicine; and ⁶Department of Anaesthesiology and Pain Medicine, Korea University College of Medicine, Seoul, Korea

Efficacy and safety of high and low molecular weight hyaluronates in knee osteoarthritis patients were compared in a randomized, open-label trial. Patients in the high molecular weight hyaluronate group were treated once weekly for 3 weeks and in the low molecular weight group once weekly for 5 weeks. We evaluated weight-bearing pain, degree of flexion, swelling and knee tenderness; frequency and amount of rescue medication; patient and investigator global assessment of pain, and safety over

12 weeks after final injection of study medication. Significant improvements in pain and WOMAC-Likert scores were observed in both groups, but not between groups. Knee joint pain improvement was noted in both groups by patients and investigators during follow-up. Close correlation was observed between patient- and investigator-reported data. There was no significant difference in side-effects between the groups. In conclusion, the efficacy and safety of high and low molecular weight hyaluronate are similar.

KEY WORDS: HYALURONATE; HIGH MOLECULAR WEIGHT; LOW MOLECULAR WEIGHT; OSTEOARTHRITIS; KNEES; ADULTS; WOMAC-LIKERT SCORES

Introduction

The elastoviscosity of synovial hyaluronate (HA) in knees depends on both its concentration and molecular weight. In osteoarthritic knees the elastoviscosity is lower than that of HA in healthy knees because of the

reduced concentration and smaller molecular weight of the synovial HA.^{1,2} High elastoviscosity is essential for knee joint lubrication and protection. Intra-articular viscosupplementation with HA can provide activity improvements and can reduce pain in patients with osteoarthritis (OA) of the knee.³⁻⁵

Two different molecular weight hyaluronates in OA knees

Many animal studies⁶⁻⁹ have shown that higher molecular weight (HMW) HAs have beneficial effects on knee joints. Clinical studies¹⁰⁻¹⁴ have also produced excellent results for HMW HA in OA knees. Data are still lacking, however, and no consensus has been reached on the relationship between therapeutic efficacy and safety of HA treatment with respect to molecular weight. After analysing published clinical results, Aviad and Houpt¹⁵ suggested that the beneficial effect of injected HA might be due to pharmacological rather than physical properties. Wobig *et al.*¹² reported that HMW HA had a significantly greater pain-relieving effect than low molecular weight (LMW) HA ($P < 0.05$), without causing adverse systemic events.

Clinically, HMW HA is now widely used, especially in Europe and the USA, and its popularity continues to grow. The molecular weight of HMW HA is similar to that of HA in synovial fluid of healthy knee joints, which contains HA of molecular weight between 2000 and 10 000 kD.^{2,16-18} Therefore, HMW HA may be more physiologically effective than LMW HA, although few studies have compared the efficacy of these two treatments.

The present study was designed to compare the efficacy of HMW HA and LMW HA administered by injection in patients with OA of the knee. In their well-designed, double-blind study, Wobig *et al.*¹² compared the efficacy and safety of HMW HA and LMW HA by injecting both HAs weekly for 3 weeks, but the US Food and Drug Administration (FDA) recommends that HMW HA should be injected once a week for 3 weeks, and LMW HA once a week for 5 weeks. We, therefore, compared the efficacy of HMW HA and LMW HA injection in our study according to the regimens recommended by the US FDA. Correlation

between the pain scores reported by patients and those assessed by study-blinded investigators were used to check for reliability, given the different number of injections between the two HAs and the open-label nature of this study.

Most of the HA products on the market have excellent safety profiles,¹⁰⁻¹⁴ but any complications associated with HA injections are likely to be proportional to injection frequency. Thus, we hypothesized that HMW HA injections would present a lower risk of side-effects than LMW HA injections because of the lower number of injections required.

Patients and methods

PATIENTS

After obtaining local Research Ethics Committee approval and written informed consent from subjects, the present randomized, open-label study was conducted at four centres from 2 February 2003 to 19 November 2003. Patients were included if they were over 40 years of age and had a diagnosis of OA of one or both knees, with radiologically verified grade I - III OA according to the Kellgren and Lawrence scale. Other inclusion criteria included failure to respond adequately to conservative treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics, and a reading of more than 30 on the 100-mm visual analogue scale (VAS) of weight-bearing pain.

Exclusion criteria were: rheumatoid arthritis or other types of inflammatory OA of metabolic origin, knee joint infections, symptomatic OA of other joints (such as hips), injection-site infection, a known hypersensitivity to the study drugs or local anaesthetics, or evidence of serious cardiac, hepatic (aspartate aminotransferase or alanine aminotransferase \geq twice that of the upper limit of the normal range), or renal

Two different molecular weight hyaluronates in OA knees

(serum creatinine ≥ 2 mg%) disorders. All subjects who took NSAIDs or other analgesics (except paracetamol [acetaminophen]) or who had received other treatments such as physical therapy or an intra-articular injection of corticosteroid or other drugs into the knee within the 3 months prior to study commencement were also excluded. Pregnant or breastfeeding women were excluded. Rescue medication was restricted to paracetamol throughout the study period.

PROCEDURE AND INSTRUMENTS

Patients who signed the consent form and met all of the above inclusion criteria underwent a 2-week washout period, during which they were required to discontinue any OA medications. Patients were not allowed to use any medications or physiotherapy until the study end. Patient eligibility was re-confirmed during a baseline visit following

the washout period. Eligible patients were then randomly assigned to one of two treatment groups: the HMW group (Hyruan Plus[®], average MW 3000 kD; LG Life Sciences Ltd, Korea) and the LMW group (Hyal[®], average MW 750 kD; Shin Poong Pharm. Co., Ltd, Korea). The HMW group was treated for 3 weeks and the active control, LMW group, was treated for 5 weeks. The study design is summarized in Fig. 1.

Overall weight-bearing pain was evaluated at baseline and at each visit. At these visits, patients conducted a self-assessment using a 100-mm VAS. Changes in WOMAC-Likert scores, physical examinations of target knees and the frequency and amounts of rescue medication were also evaluated at baseline and at 1, 6 and 12 weeks after final injection. Patient and investigator global assessments of pain were evaluated using a 100-mm VAS, 1 and 12 weeks after the final

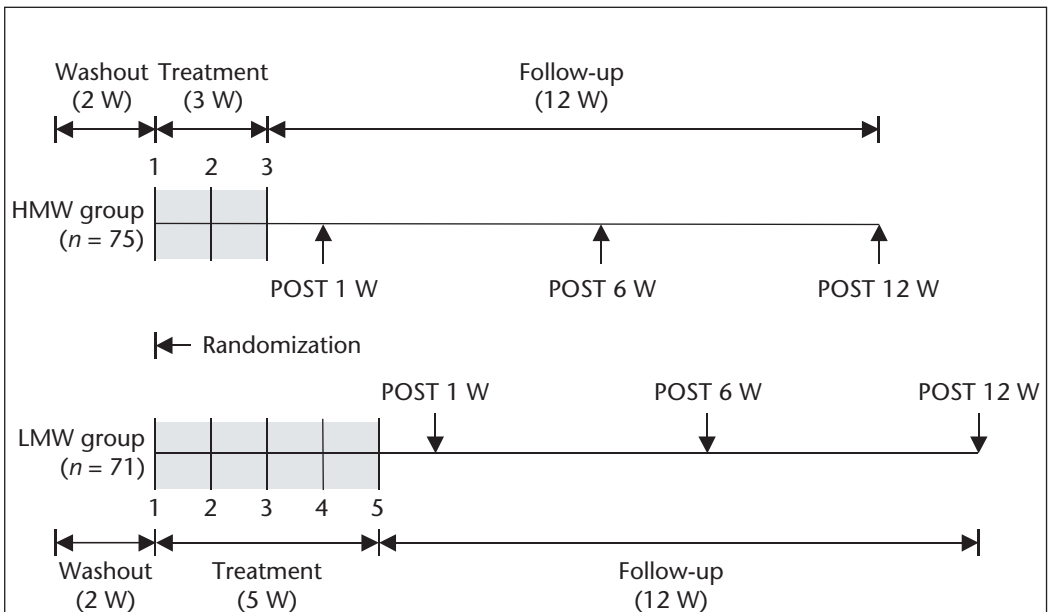


FIGURE 1: Design of 17-week randomized study to compare high molecular weight (HMW) with low molecular weight (LMW) hyaluronates in 146 patients with osteoarthritic knees. The LMW group served as the active control

Two different molecular weight hyaluronates in OA knees

injection. Study-blinded investigators performed a physical examination of target knees and carried out global assessments of pain improvement. Degree of flexion, swelling and tenderness were assessed using four grades: none; mild; moderate; and severe. Average efficacy and incidence of side-effects for both knees were evaluated if a patient had bilateral knee OA and both knees fulfilled the selection criteria.

Adverse events and clinical laboratory results were evaluated as safety variables. Information was collected on all adverse events observed during the study period regardless of their possible relationship to study medication. Relationships between study regimens and adverse events were judged by study-blinded investigators and ranked as follows: unrelated; possibly unrelated; possibly related; probably related; and definitely related. Clinical laboratory results were obtained from blood and urine samples collected during the washout period and again 1 week after treatment completion.

STATISTICAL ANALYSIS

The planned sample size was calculated by non-inferiority testing as described previously^{12,19} with 100-mm VAS as primary efficacy variable. The margin of non-inferiority (10 of 100-mm VAS) was inferred from both the difference of the improvement between the superior effect¹² and inferior effect,¹⁹ which was 10 of 100-mm VAS and the half of the difference between test drug and placebo (12 – 24 of 100-mm VAS).^{12,19} The calculated sample size per group was 58 for a type I error of 0.05 and statistical power of 80%. Thus, assuming a 20% dropout rate, our target enrolment was 73 patients per group.

Specific randomization codes were generated and stratified at each centre using

the block randomization method to avoid clinically significant differences in demographic characteristics between the two groups. Blocks containing 4 and 6 codes had been mixed. The order of these blocks had been determined by randomization.

Demographic characteristics of the two groups were compared using the *t*-test, the χ^2 test, or Fisher's exact test. Differences between the two groups in terms of VAS scores for weight-bearing pain and WOMAC-Likert scores were analysed by longitudinal data analysis using repeated-measures analysis of covariance. One-way repeated-measures analysis of variance, followed by Dunnett's method, was used for intragroup comparisons.

Comparisons of overall improvement of knee joint pain in both patient and investigator global assessments between and within groups were performed using the *t*-test and paired *t*-test, respectively. Correlations between patient and investigator pain data were made using the Spearman rank order correlation method.

Intergroup and intragroup comparisons of major signs of swelling, tenderness and range of motion in target knee joints were compared using the generalized estimating equation method and χ^2 test, respectively. The numbers of patients in the two groups who had taken paracetamol as a rescue medication during the study and the mean doses taken were compared using the χ^2 or Fisher's exact tests and *t*-test, respectively. The relationship between the presence or absence of paracetamol medication during the study period and weight-bearing pain were compared using the *t*-test and the paired *t*-test for intergroup and intragroup comparisons, respectively.

Adverse events possibly related to the administration of HA were compared using χ^2 or Fisher's exact tests. *P*-values < 0.05 were considered statistically significant.

Two different molecular weight hyaluronates in OA knees

Results

Two hundred and thirty-eight patients were enrolled, of whom 157 were randomly assigned to study treatments: 79 to the HMW group and 78 to the LMW group. Of these, 11 patients (four in the HMW group and seven in the LMW group) were withdrawn prematurely from the study: two patients in the HMW group and three patients in the LMW group for treatment refusal or failure to

provide consent, and other reasons for withdrawal were adverse events and protocol deviations. One hundred and forty-six patients completed the study: 75 in the HMW group and 71 in the LMW group. Forty-three patients in the HMW group and 47 patients in the LMW group received intra-articular injections in both knees, and thus the study included 118 knees in each group. Patient demographic characteristics were similar in the two groups and are summarized in Table 1.

TABLE 1: Baseline characteristics of the patients with knee osteoarthritis (OA) enrolled in a study comparing high molecular weight (HMW) and low molecular weight (LMW) hyaluronates

	HMW group <i>n</i> = 75 (%)	LMW group <i>n</i> = 71 (%)
Gender (male/female)	5/70 (7/93)	4/67 (6/94)
Age (years)	59.6 ± 8.8	61.1 ± 7.4
Height (cm)	155 ± 7	155 ± 6
Weight (kg)	63 ± 10	63 ± 9
Body mass index (kg/cm ²)	26 ± 3	26 ± 3
OA (R/L/B)	19/13/43 (26/17/57)	16/8/47 (23/11/66)
Number of injected knees	118	118
OA duration (≥ 3 years/< 3 years)	32/43 (43/57)	35/36 (49/51)
Previous treatment		
Medication		
Paracetamol	39 (52)	40 (56)
NSAIDs	24 (32)	26 (37)
Physical therapy	11 (15)	5 (7)
Past history		
Hypertension	19 (25)	24 (34)
Diabetes mellitus	2 (3)	6 (8)
Osteoporosis	3 (4)	6 (8)
Others	7 (9)	8 (11)
Concomitant medication ^a	49 (65)	56 (79)

Data are mean ± SD or number (%) of patients.

^aConcomitant medication (paracetamol) during the study period.

R/L/B, right/left/bilateral; NSAIDs, non-steroidal anti-inflammatory agents.

Two different molecular weight hyaluronates in OA knees

The changes in weight-bearing pain VAS scores were not significantly different between the two groups. Both groups showed a significant reduction in pain from baseline ($P < 0.0001$). Mean pain reduction from baseline to 12 weeks after the final injection was approximately 26 mm ($P < 0.0001$) in the HMW group and 27 mm ($P < 0.0001$) in the LMW group (Fig. 2).

Both groups showed significant improvements in all WOMAC-Likert scores (pain, function and stiffness) from baseline during the follow-up period ($P < 0.0001$), but no differences were observed between the groups (Fig. 3).

Overall knee joint pain improvements were noted in both groups according to patient and investigator global assessments during the follow-up period, although no significant inter-group difference was found (Fig. 4). A close correlation was found between the data reported by patients and

those reported by investigators (correlation coefficient = 0.809 – 0.954, $P = 0.000$). The major signs of OA (including swelling, tenderness and range of motion in target knee joints [flexion]) were improved in both groups ($P < 0.0001$) (Table 2).

The numbers of patients who had taken paracetamol as a rescue medication during the study were calculated. In the HMW group, 39 patients (52%) used paracetamol (mean total dosage per patient $23\,295 \pm 22\,601$ mg) and in the LMW group, 39 patients (56%, mean total dosage per patient $30\,073 \pm 39\,731$ mg). Patients who did not receive paracetamol as a rescue medication during the study period showed significantly higher weight-bearing pain relief than those who had taken rescue medication more than once. Net changes in weight-bearing pain scores (100-mm VAS) from baseline to week 12 after the final injection were 33 ± 22 mm (mean \pm SD) and

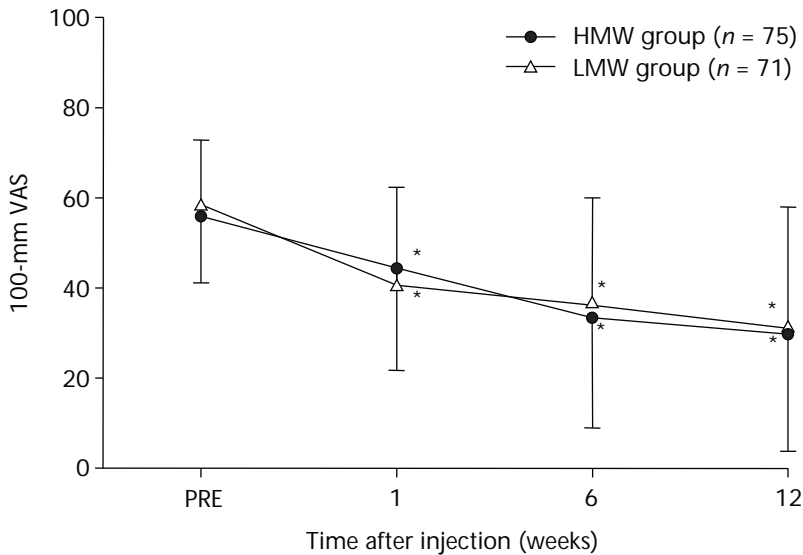


FIGURE 2: Change from baseline (PRE) to endpoint in weight-bearing pain score in 146 patients with osteoarthritic knees given either high molecular weight (HMW) or low molecular weight (LMW) hyaluronates. Data are expressed as the mean \pm SD of 100-mm visual analogue scale (VAS). * $P < 0.0001$

Two different molecular weight hyaluronates in OA knees

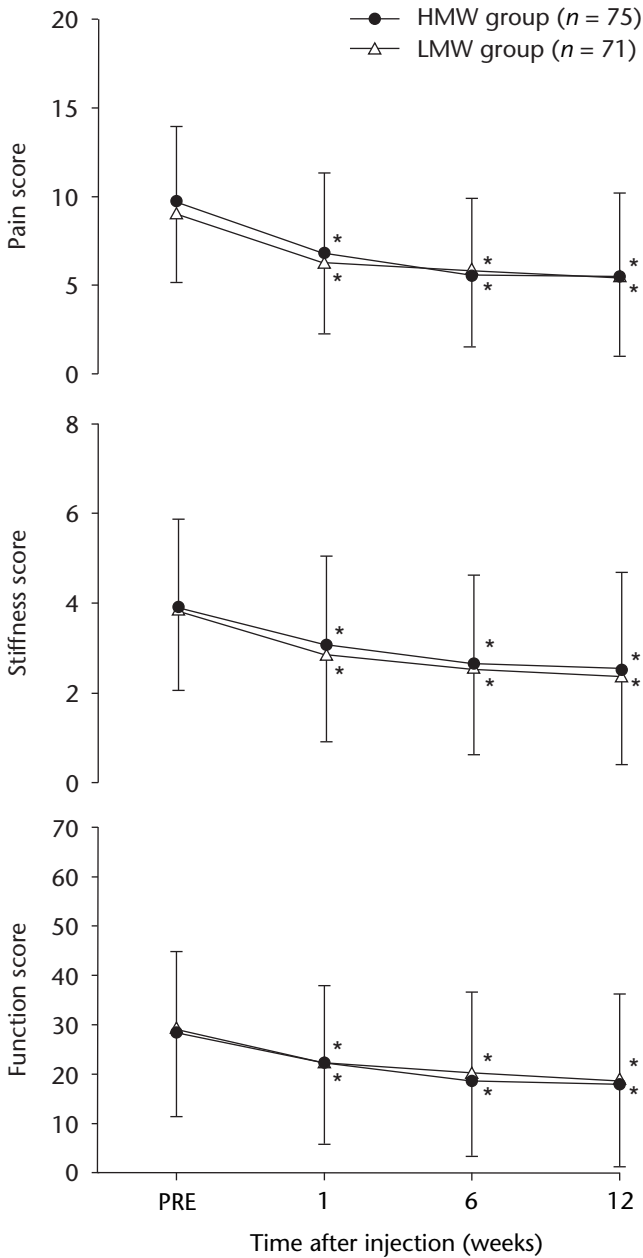
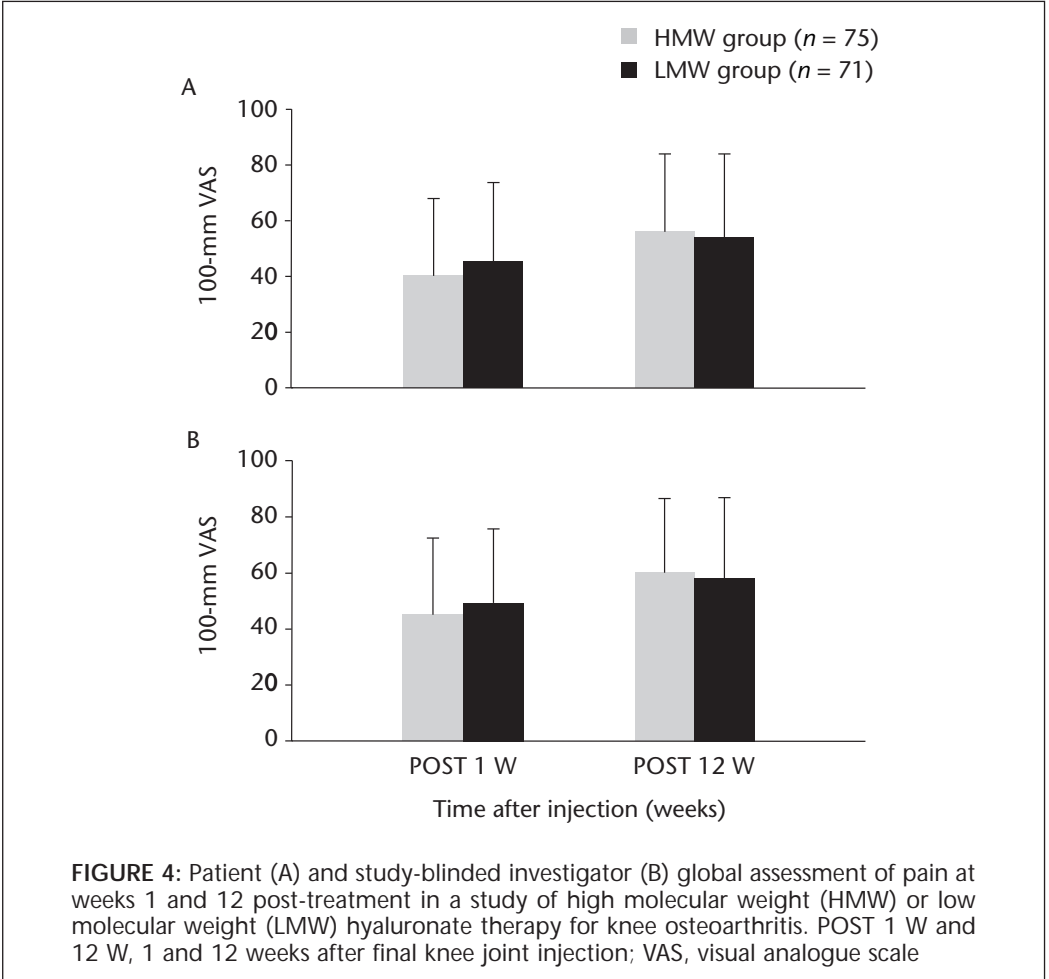


FIGURE 3: Change from baseline (PRE) to endpoint in WOMAC-Likert pain, function, and stiffness scores in 146 patients with osteoarthritic knees given either high molecular weight (HMW) or low molecular weight (LMW) hyaluronates. Data are expressed as the mean ± SD. **P* < 0.0001

Two different molecular weight hyaluronates in OA knees



20 ± 22 mm (mean ± SD) in patients who did not take or who took paracetamol respectively, in the HMW group ($P = 0.008$). Corresponding results in the LMW group were 38 ± 23 mm (mean ± SD) and 19 ± 26 mm (mean ± SD), respectively ($P = 0.002$).

Twenty-three patients (31%) in the HMW group and 25 (35%) in the LMW group reported one or more adverse events that were judged by the authors to be possibly related to HA administration. The most common adverse event in both groups was pain at the injection site, affecting 23 patients (31%) in the HMW group and 24 (34%) in the LMW group. One patient

experienced myalgia, one urticaria, and one pruritus in each of the two groups. In addition, in the HMW group, one patient had arthrosis and one had high-sensitivity C-reactive protein (hs-CRP) elevation. In the LMW group, three showed paraesthesia, one leg pain, one calf pain, one contact dermatitis and one leucopenia. All events resolved without any complication by the end of the study (12 weeks after the final injection).

In both treatment groups, a small number of patients showed clinically significant haematology and blood biochemistry abnormalities, which were not considered to

Two different molecular weight hyaluronates in OA knees

TABLE 2:
Findings of physical examination of injected knees in patients with knee osteoarthritis receiving treatment with either high molecular weight (HMW) or low molecular weight (LMW) hyaluronates

	HMW group (n = 118)	LMW group (n = 118)	P-value
Swelling			0.6649
PRE (Yes/No)	77/41	80/38	NS
POST 12 W (Yes/No)	25/93 ^a	29/89 ^a	NS
Tenderness			0.6714
PRE (Yes/No)	89/29	96/23	NS
POST 12 W (Yes/No)	45/73 ^a	45/73 ^a	NS
Flexion			0.7847
PRE ($\geq 135^\circ < 135^\circ$)	41/77	41/77	NS
POST 12 W ($\geq 135^\circ < 135^\circ$)	25/93 ^a	36/88 ^a	NS

Data are number of injected knees.

^a $P < 0.0001$ versus PRE.

PRE, baseline; POST 12 W, 12 weeks after the final knee joint injection; NS, not significant.

be study related and resolved spontaneously with no complications.

Discussion

The present study shows that HMW and LMW HAs are of similar efficacy in treating knee OA. Our findings contradict those of Wobig *et al.*,¹² who reported that patients administered hyalgan G-F 20 (Synvisc®, Biomatrix, Inc., Ridgefield, NJ, USA; HMW HA) showed significantly ($P < 0.05$) better results for all primary outcome measures as well as overall assessment of treatment when compared with those receiving LMW HA. These contrasting results are attributed to the different number of injections of LMW HA administered. In the Wobig *et al.*¹² study, LMW HA and HMW HA were both administered once a week for 3 weeks for the double-blind study protocol; however, this was not in accord with pharmacopoeia-recommended injection regimens. Therefore, in the present study we chose an open-label method, rather than a

double-blind method, to compare the efficacy of these two different molecular weight HAs under therapeutic conditions despite the fact that there might be a possibility of bias. To ensure the reliability of the results obtained from our open-label study and the different number of injections between the two HAs, we analysed the correlations between pain scores reported by patients and those assessed by study-blinded investigators and found close correlation between the two. We believe that the open-label design and the different injection regimen adopted in the present study had only a minor effect on the results.

No significant differences were observed between the two groups in terms of side-effects. The most commonly reported adverse event was injection-site pain, which occurred in both treatment groups at a similar frequency. Although HMW HA injections might be considered to have higher risks of post-injection allergic reactions due to the HA molecular weight, we believed originally

that HMW HA injections would be less associated with complications than LMW HA injections due to the lower number of injections required. It is certainly true that the greater the number of times that HA is injected into the knee joint, the higher the chance of joint infection. The results show, however, that overall adverse-event profiles were not significantly different and no serious adverse effects (such as joint infection) were observed. As potentially serious adverse events are rare, large population studies will be required in any further work. The incidence and severity of adverse events observed in this study were also similar to those reported in other clinical studies involving various HA types.¹⁰⁻¹⁴ Serious adverse effects in relation to therapy are one of the most important considerations when selecting a therapeutic strategy. Thus, we consider that the clinical use of the newly introduced HMW HA, Hyruan Plus[®], is not problematic with regards to safety. In addition, this formulation could provide less patient discomfort because of the lower frequency of injections than needed with LMW HA therapy. Although we did not observe any serious adverse events in the two different HAs, HMW HA might be anticipated to have a lower risk of serious adverse events because it requires fewer

injections than LMW HA.

We conclude that the efficacy and safety of HMW HA administered once a week for 3 weeks is comparable to that of LMW HA administered once a week for 5 weeks and that, by reducing injection frequency, patient discomfort will probably be reduced.

Acknowledgements

Support for this study was provided by a grant from LG Life Sciences (HACL003).

We thank Hyonggi Jung, PhD, for performing the statistical analysis. In addition, we also thank Dr Jae-Sang Sung and Pharmacists Soo-Hee Paik and Seung-Yoon Song of the Seoul National University Hospital; Drs Ki-Sun Sung and Jun-Ho Wang and Pharmacists Hyun-In Cho, Jung-Hyun Kim, and Shin-Han Chung of the SungKyunKwan University Samsung Medical Centre; Dr Hong-jae Lee and Pharmacists Han-Jung Yoon and Ji-Won Cho of the Inje University Ilsan-paik Hospital; Dr Dong-Man Choo and Pharmacists Si-Hyun Park and Sook-Hee Ahn of the Ulsan University Asan Medical Centre; and Pharmacist Hye-won Song of the LG Life Sciences for their help on this study.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

• Received for publication 19 July 2005 • Accepted subject to revision 5 August 2005

• Revised accepted 23 September 2005

Copyright © 2006 Cambridge Medical Publications

References

- Balazs EA, Watson D, Huff IF, Roseman S: Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. *Arthritis Rheum* 1967; **10**: 357 - 376.
- Dahl LB, Dahl IM, Engstrom-Laurent A, Granath K: Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann Rheum Dis* 1985; **44**: 817 - 822.
- 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.
- Marshall KW: Intra-articular hyaluronan therapy. *Curr Opin Rheumatol* 2000; **12**: 468 - 474.
- Uebelhart D, Williams JM, Uebelhart D, Williams JM: Effects of hyaluronic acid on cartilage degradation. *Curr Opin Rheumatol* 1999; **11**: 427 - 435.

Two different molecular weight hyaluronates in OA knees

- 6 Kikuchi T, Yamada H, Shimmei M: Effect of high molecular weight hyaluronan on cartilage degeneration in a rabbit model of osteoarthritis. *Osteoarthritis Cartilage* 1996; **4**: 99 - 110.
- 7 Sakakibara Y, Miura T, Iwata H, Kikuchi T, Yamaguchi T, Yoshimi T, *et al.* Effect of high-molecular-weight sodium hyaluronate on immobilized rabbit knee. *Clin Orthop Relat Res* 1994; **299**: 282 - 292.
- 8 Yoshimi T, Kikuchi T, Obara T, Yamaguchi T, Sakakibara Y, Itoh H, *et al.* Effects of high-molecular-weight sodium hyaluronate on experimental osteoarthritis induced by the resection of rabbit anterior cruciate ligament. *Clin Orthop Relat Res* 1994; **298**: 296 - 304.
- 9 Gomis A, Pawlak M, Balazs EA, Schmidt RF, Belmonte C: Effects of different molecular weight elastoviscous hyaluronan solutions on articular nociceptive afferents. *Arthritis Rheum* 2004; **50**: 314 - 326.
- 10 Lussier A, Cividino AA, McFarlane CA, Olszynski WP, Potashner WJ, De Medicis R: Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol* 1996; **23**: 1579 - 1585.
- 11 Wöbig M, Dickhut A, Maier R, Vetter G: Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther* 1998; **20**: 410 - 423.
- 12 Wöbig 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.
- 13 Adams ME, Atkinson MH, Lussier AJ, Schulz JL, Siminovitch KA, Wade JP, *et al.* The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicentre trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage* 1995; **3**: 213 - 225.
- 14 Adams ME: An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. *J Rheumatol Suppl* 1993; **39**: 16 - 18.
- 15 Aviad AD, Houpt JB: The molecular weight of therapeutic hyaluronan (sodium hyaluronate): how significant is it? *J Rheumatol* 1994; **21**: 297 - 301.
- 16 Laurent TC, Fraser JR: Hyaluronan. *FASEB J* 1992; **6**: 2397 - 2404.
- 17 Ghosh P, Guidolin D: Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? *Semin Arthritis Rheum* 2002; **32**: 10 - 37.
- 18 Fraser JR, Laurent TC, Laurent UB: Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med* 1997; **242**: 27 - 33.
- 19 Altman RD, Moskowitz R: Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. *J Rheumatol* 1998; **25**: 2203 - 2212.

Address for correspondence

Dr YC Kim

Department of Anaesthesiology and Pain Medicine, Seoul National University College of Medicine, 28 Yeongeon-dong, Chongno-ku, Seoul, 110-744 Korea.

E-mail: pain@snu.ac.kr