

Effects of Hyaluronate Sodium on Pain and Physical Functioning in Osteoarthritis of the Knee

A Randomized, Double-blind, Placebo-Controlled Clinical Trial

Robert John Petrella, MD, PhD; Mathew Dennis DiSilvestro, MSc; Catherine Hildebrand, PhD

Background: Intra-articular hyaluronate sodium is a relatively new therapy for the treatment of osteoarthritis of the knee. This randomized, double-blind clinical trial was conducted at a large primary care medical center to determine the impact of hyaluronate sodium vs conventional therapy on measures of pain, stiffness, and disability at rest and following functionally relevant walking and stepping activities.

Methods: A total of 120 patients (mean age, 67 years) with unilateral grades 1 to 3 medial compartment knee osteoarthritis were randomized to 1 of 4 treatment groups: group 1, 2 mL of hyaluronate sodium at a concentration of 10 mg/mL and placebo (100 mg of lactose); group 2, nonsteroidal anti-inflammatory drugs (NSAIDs) (75 mg of diclofenac and 200 µg of misoprostol) and hyaluronate sodium; group 3, NSAIDs and placebo (2 mL of isotonic sodium chloride solution [saline]); and group 4, placebo (lactose and saline). Intra-articular hyaluronate sodium or saline (2 mL) was administered once weekly over 3 weeks while NSAIDs or lactose were administered twice daily over 12 weeks.

Main Outcome Measures: (1) Western Ontario McMaster Universities Index (WOMAC) global measure of pain, stiffness, and disability; (2) visual analog scale (VAS) scores for pain at rest and following functional walking and stepping activities (self-paced walking and stepping); and (3) functional performance

(exercise time, heart rate, and predicted maximum oxygen uptake) at baseline and weeks 4 and 12.

Results: At week 4, significant improvement in WOMAC scores for pain and disability and VAS score for resting pain was observed in groups 1 to 3 compared with baseline measures. Groups 1 and 2 showed significantly lower self-paced stepping pain, while no change was observed in group 4. At week 12, groups 1 to 3 showed significantly greater improvement in WOMAC pain subscale score and VAS score for resting pain; however, these differences did not vary from week 4. Following self-paced walking and stepping, groups 1 and 2 reported significantly less activity pain, while group 1 showed significantly faster self-paced walking and stepping test results. Groups 1 to 3 improved self-paced walking and stepping time at week 12 compared with baseline measures, while predicted maximum oxygen uptake was significantly higher in the hyaluronate sodium groups 1 and 2 at weeks 4 and 12 compared with baseline measures.

Conclusions: For resting pain relief, hyaluronate sodium seems to be as effective as NSAIDs. Further, for pain with physical activity and functional performance, hyaluronate sodium may be superior to placebo alone or NSAIDs alone.

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From the Centre for Activity and Ageing, Lawson Research Institute and Faculties of Medicine and Health Sciences, University of Western Ontario, London (Dr Petrella); the Faculty of Medicine, University of Calgary, Calgary, Alberta (Mr DiSilvestro); and Bioniche Life Sciences Inc, Belleville, Ontario (Dr Hildebrand).

DESPITE the increasing morbidity and economic costs of osteoarthritis (OA),¹ standard therapies have not progressed significantly over the past several years. Current therapies are directed at controlling pain and maintaining articular function rather than altering physical functioning and the disease process.² Osteoarthritis is the result of mechanical and biological events that destabilize the normal degradation synthesis of articular cartilage.^{3,4} Hyaluronic acid (HA) is a major component of the articular matrix, assuming an important role in its viscoelastic structural and functional balance.⁴

Osteoarthritis is characterized by a decrease in the concentration and molecular weight of HA,⁵ which may lead to the hallmark signs of pain and loss of function in weight-bearing joints such as the

*For editorial comment
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knee.⁶ Intra-articular viscosupplementation may restore the concentration and molecular weight of HA in the articular matrix, resulting in improved pain control and function.⁵ Hence, HA may provide clinicians with a novel approach to address the clinical course of OA. Further, the pos-

SUBJECTS AND METHODS

SUBJECTS

Patients were recruited from a large primary care referral center (Centre for Activity and Ageing, London, Ontario) for assessment of knee OA. The study was approved by the University of Western Ontario ethics review board. Those with radiographic evidence of grades 1 to 3 medial compartment unilateral knee OA,⁷ but who did not exhibit non-OA arthritides, previous nonsteroidal anti-inflammatory drug (NSAID) intolerance, gastrointestinal hemorrhage, peptic ulcer disease, avian allergy, regular consumption of "herbal" OA products (ie, glucosamine sulfate), or an intra-articular injection of HA or corticosteroid in the previous 6 months were given a screening examination with their consent. Patients were also asked to discontinue all current OA medications and were scheduled to return 2 weeks later for baseline outcome assessments (see the following section) in addition to demographic data collection (age, sex, body mass index [BMI]), and comorbidities). Those who displayed grades 1 to 3 OA on radiographs and who described at least 3-cm current rest pain using a visual analog scale (VAS) (see "Outcome Measures" section below) at baseline were included.

OUTCOME MEASURES

We included measures of pain at rest and following a functional task. Measures of physical functioning and global assessment of pain and physical functioning as recommended in the literature were also included.⁸

Pain

The primary outcome measure of pain was determined in 2 ways: (1) self-report of current pain (CP) using a VAS⁹ and (2) the pain subscale of the Western Ontario McMaster Universities Index (WOMAC)⁸ using the VAS format. In brief, the CP-VAS consisted of a 10-cm horizontal line anchored with descriptors of pain including "no pain" on one end (left) and "extreme pain" on the other (right). After sitting for 10 minutes, subjects struck a vertical line through the 10-cm VAS representing their CP, and the distance from left end (no pain) to the vertical line was recorded in centimeters. The WOMAC

consists of 24 questions: 5 determine subject global assessment of pain, 2 assess joint stiffness, and 17 assess physical functioning. A 10-cm horizontal VAS line with anchored descriptors such as "no pain" or "no stiffness" at one end and "extreme pain" or "extreme stiffness" at the other end was used to score responses. The WOMAC was completed following a 10-minute rest. Individual scores for pain, stiffness, and physical functioning were generated by summing the appropriate terms.

Activity-related pain measures were determined by completion of the CP-VAS immediately following 2 physical activity tests (see the "Physical Functioning" section below). These tests were separated by 15 minutes or until the time the CP-VAS score returned to the baseline value.

Physical Functioning

Physical functioning was determined in 2 ways: (1) the stiffness and physical disability subscales of the WOMAC and (2) functional performance of a self-paced walking (SPW) test¹⁰ and a self-paced stepping (SPS) test.¹¹ The WOMAC global assessments have been described above in the "Pain" section. In brief, the SPW consisted of a 40-m walk at a pace chosen by the subject to reflect a "normal" or comfortable pace, and the SPS consisted of stepping up and down small (9.5 in [24.13 cm]) steps 20 times at a similar normal or comfortable pace. Data collected following these activities included time in seconds and heart rate. These data, along with age, sex, and BMI, were used to predict the metabolic cost of the activity or oxygen uptake (VO_2max).¹¹ The psychometric properties of these predictive tests have been previously reported.^{10,11} The SPW and SPS tests were administered in random order and separated by at least 15 minutes.

DEMOGRAPHIC AND CLINICAL VARIABLES

Information on age, sex, comorbidities, and medications were obtained by self-report, medical history, and physical examination. Osteoarthritis in joints other than the index knee was defined as a physician having told the subject he or she had OA in the hands, spine, hips, or feet. Other

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sible mechanical improvement of the intra-articular matrix may provide added benefit for pain control during functional activity of the knee. This study was undertaken to determine the effect of treatment with hyaluronate sodium compared with standard therapy and placebo for pain relief and physical functioning in patients with OA of the knee over 12 weeks.

RESULTS

Recruitment of participants was conducted over 6 months. The study sample comprised 120 individuals (71 women and 49 men), who provided informed consent and were screened and randomized into 1 of 4 study groups. Of the subjects, 58% presented with right knee OA. Twelve subjects failed to complete the

study: 1 was lost to follow-up; 2 had moderate gastrointestinal irritation; 1 failed to comply with study tablet protocol; and 8 dropped out without reason prior to treatment (after randomization). In the study sample, severity of OA was grade 1 for 23%, grade 2 for 45%, and grade 3 for 32%. The characteristics of all the participants are shown in **Table 1**. There were neither statistically significant differences among the 4 groups nor differences in the dropouts among groups for demographic characteristics, baseline physical functioning, or grade of OA.

Overall compliance with the exercise program (at week 12) was 76% in group 1, 70% in group 2, 77% in group 3, and 71% in group 4. Compliance with the exercise interventions overall declined during the trial: 85% at week 4 to 75% at week 12. There was no statistically

chronic diseases including hypertension, coronary artery disease, and diabetes mellitus were defined as self-report and clinical confirmation with or without current use of medications for that condition.

Height and weight were measured by a standard protocol and BMI was calculated as weight in kilograms divided by the square of height in meters. Standing anterior-posterior knee radiographs were obtained at baseline and week 12 to confirm grades 1 to 3 OA and to determine the treatment effects on radiographic disease. Films were read by a single radiologist masked to treatment group assignment and timing of the radiograph. The classification scheme⁷ included grading of both medial and lateral compartments for osteophytes, subchondral sclerosis, subchondral cysts, and loss of joint space. Passive range of motion was determined as the total degrees of flexion from full extension using a standard handheld goniometer.

TREATMENTS

Two milliliters of intra-articular sodium hyaluronate solution at a concentration of 10 mg/mL (Suplasyn; Bio-niche Life Sciences Inc, Belleville, Ontario) or placebo (2 mL of isotonic sodium chloride solution [saline]) was injected under sterile field using a medial approach at baseline and weeks 2 and 3 by a blinded physician. From baseline to week 12, NSAIDs (75 mg of oral diclofenac and 200 µg of misoprostol [Arthrotec; Pharmacia Inc, Peapack, NJ]) or placebo (100 mg of lactose) were ingested twice daily. Subjects were also given 325 mg of acetaminophen as rescue medication to be taken as needed up to 650 mg 4 times daily.

STUDY DESIGN

Following baseline assessments, subjects were randomized by computer program to 1 of the following 4 groups: group 1, hyaluronate sodium and placebo tablet; group 2, NSAIDs and hyaluronate sodium; group 3, NSAIDs and placebo injection; and group 4, placebo tablet and placebo injection. Injections were administered following all outcome assessments at baseline and weeks 1 and 2. At baseline, all subjects were also given instructions regarding a 10-minute home-based resistance exercise program^{12,13} by a blinded kinesiologist. An accompanying videotape was made

available to assist with the exercises that were to be performed at least 3 (but preferably on most) days of the week and recorded in a patient log. At week 3, subjects returned to the clinic for outcome measures only and were scheduled for a 12-week follow-up visit. Oral study medications as well as regular-strength (325 mg) acetaminophen for rescue analgesic purposes were also dispensed at this time. All data were collected by staff masked to treatment assignments.

STATISTICAL ANALYSIS

Pain reduction using the WOMAC global assessment was the primary outcome measure. The trial was designed to randomize 30 subjects to each intervention group to achieve at least 25 subjects in each group at the end of 12 weeks. A study sample of 100 was projected to provide a power of 0.8 to detect a 20% difference in pain reduction among groups.

Primary analyses were conducted by intent to treat with participants analyzed according to the initial randomized assignments. All tests of hypotheses and reported *P* values are 2-sided. Post hoc secondary analyses were performed to examine outcomes by subgroup (age, sex, BMI, and more than 1 comorbidity).

Analysis of variance and the χ^2 test were used to test for differences in baseline characteristics by treatment group. The effects of treatments on pain and physical functioning measured at weeks 4 and 12 were determined by repeated-measures analysis of covariance. Analyses were conducted using Sigma Stat (SPSS Inc, Chicago, Ill) and Microsoft Excel (Microsoft Corp, Redmond, Wash).

Analyses of group differences were adjusted for the pre-randomization level of baseline factors used in the blocked randomization to provide the correct variance estimates for the randomization design. The analyses were also adjusted for prerandomization values of other factors (ie, SPW and SPS time, predicted $\dot{V}O_{2max}$, BMI, and WOMAC physical disability score). All values were significantly associated with the outcome variables after adjusting for the other terms in the model. The baseline value of the outcome of interest was also included in the analyses. The frequency of adverse events in each group was evaluated with the χ^2 statistic to establish a safety profile for the various treatments.

significant difference in the decline in compliance with the exercise program among the 4 groups.

No serious adverse events occurred during the study. It is interesting that most adverse events were reported in group 3, although this was not statistically significant.

MAIN OUTCOMES

Pain

The primary outcome in the trial was self-reported pain using the WOMAC global assessment. Baseline measures of pain were similar in all 4 groups (**Table 2**). At week 4, groups 1 to 3 showed significant decrease in the pain subscale as reported on the WOMAC global

assessment (Table 2). At week 12, the difference in pain scores among groups compared with those at baseline were unchanged from week 4 in groups 1 and 3 but was significantly greater in group 2 (*P* = .005).

Pain at rest using the VAS was significantly reduced in all groups at week 4 (**Table 3**). There was no further pain reduction from weeks 4 to 12.

Physical Functioning, Stiffness, and Pain With Activity

Groups 1 to 3 showed significant (*P* < .05) improvement in the WOMAC global assessment of physical disability at week 4, while groups 1 and 2 showed further significant (*P* < .05) improvement from weeks 4 to 12 (Table 2). The WOMAC global assessment of stiffness

Table 1. Subject Demographic Characteristics*

Characteristic	All Subjects (N = 120)	Group 1: Hyaluronate Sodium + Placebo (n = 25)	Group 2: NSAIDs + Hyaluronate Sodium (n = 29)	Group 3: NSAIDs + Saline† (n = 26)	Group 4: Control (n = 28)	Dropouts (n = 12)
Age, y	65.5 ± 9.0	67.3 ± 8.9	65.0 ± 9.7	66.3 ± 8.8	62.6 ± 9.5	65.2 ± 8.4
Female sex, No.	55	9	13	11	12	10
OA grade‡	2.2 ± 0.3	2.5 ± 0.6	2.2 ± 0.5	2.3 ± 0.4	2.3 ± 0.4	2.2 ± 0.2
Chronic diseases§	1 ± 1.1	1 ± 0.9	2 ± 0.9	1 ± 1.0	1 ± 1.2	2 ± 1.5
BMI, kg/m ²	30.7 ± 5.6	29.5 ± 4.2	31.6 ± 6.3	29.4 ± 6.3	32.7 ± 4.8	29.7 ± 4.7

*Data are given as mean ± SD except as otherwise indicated. NSAIDs indicates nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; and BMI, body mass index.

†Placebo isotonic sodium chloride solution injection.

‡Based on classification of Altman et al.⁷

§Number of chronic disease diagnoses on medical history.

Table 2. WOMAC Subscale Indices of Pain, Disability, and Stiffness at Baseline and Week 4*

VAS-WOMAC Outcome Measures	Group 1: Hyaluronate Sodium + Placebo (n = 25)	Group 2: NSAIDs + Hyaluronate Sodium (n = 29)	Group 3: NSAIDs + Saline† (n = 26)	Group 4: Control (n = 28)
Pain				
Baseline	3.32 ± 2.42	3.65 ± 2.73	4.22 ± 3.25	3.62 ± 2.71
Week 4	2.42 ± 2.34‡	2.59 ± 2.59‡	2.86 ± 2.75‡	3.19 ± 2.81
Disability				
Baseline	4.10 ± 2.71	3.90 ± 2.72	4.32 ± 3.22	4.72 ± 3.03
Week 4	2.45 ± 2.23‡	2.73 ± 2.64‡	2.76 ± 2.61‡	3.73 ± 2.99‡
Stiffness				
Baseline	4.60 ± 2.45	4.82 ± 2.88	5.14 ± 3.21	5.12 ± 2.59
Week 4	2.95 ± 2.41‡	2.71 ± 2.70‡	2.80 ± 2.72‡	5.00 ± 2.94

*Data are given as mean ± SD in centimeters. WOMAC indicates Western Ontario McMaster Universities Index; VAS-WOMAC, visual analog scale for WOMAC; and NSAIDs, nonsteroidal anti-inflammatory drugs.

†Placebo isotonic sodium chloride solution injection.

‡P < .05 for within-groups comparison.

Table 3. Physical Functioning and Pain at Baseline and Week 4*

VAS Outcome Measures	Group 1: Hyaluronate Sodium + Placebo	Group 2: NSAIDs + Hyaluronate Sodium (n = 29)	Group 3: NSAIDs + Saline† (n = 26)	Group 4: Control (n = 28)
Rest pain				
Baseline	3.29 ± 1.75	3.60 ± 1.85	3.34 ± 1.39	3.30 ± 1.42
Week 4	2.60 ± 1.64‡	1.56 ± 1.34‡	1.58 ± 1.34‡	1.77 ± 1.30‡
SPW pain				
Baseline	3.94 ± 2.79	3.84 ± 2.92	3.78 ± 3.42	3.53 ± 2.99
Week 4	2.89 ± 1.72‡	2.05 ± 1.32‡	1.81 ± 1.72‡	3.56 ± 1.77
SPS pain				
Baseline	3.49 ± 3.06	4.50 ± 3.29	5.17 ± 3.18	2.72 ± 2.71
Week 4	1.67 ± 1.52‡	3.12 ± 1.76‡	2.46 ± 1.41‡	2.15 ± 1.00

*Data are given as mean ± SD in centimeters. VAS indicates visual analog scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SPW, self-paced walk test; and SPS, self-paced stepping test.

†Placebo isotonic sodium chloride solution injection.

‡P < .05 for within-groups comparison.

significantly ($P < .05$) improved from baseline in all groups at week 4; however, no further improvement was observed at week 12 (Table 2). Group 2 showed a greater reduction in stiffness at week 4 but not at week 12 compared with the other groups, but this did reach statistical significance.

Pain (CP-VAS) at rest and following activity was evaluated with the SPW and SPS tests (Table 3). There were no differences in pain (CP-VAS) following either test nor differences in exercise time, exercise heart rate, or predicted $\dot{V}O_2$ max among groups at baseline. All 4 groups reported significantly ($P < .05$) less activity pain

Table 4. Physical Functioning at Baseline and Week 4*

Outcome Measures	Group 1: Hyaluronate Sodium + Placebo (n = 25)	Group 2: NSAIDs + Hyaluronate Sodium (n = 29)	Group 3: NSAIDs + Saline† (n = 26)	Group 4: Control (n = 28)
SPW time, s				
Baseline	77.23 ± 16.90	78.81 ± 23.56	77.64 ± 13.57	70.56 ± 14.79
Week 4	74.21 ± 17.43	72.22 ± 17.00‡	75.70 ± 15.63	71.07 ± 16.46
SPS time, s				
Baseline	109.54 ± 27.21	96.67 ± 32.16	111.34 ± 32.84	100.24 ± 22.74
Week 4	84.16 ± 18.87‡	92.90 ± 31.30	97.18 ± 23.61	90.42 ± 13.62
$\dot{V}O_2$ max, mL/kg per minute				
Baseline 1-SPW	22.1 ± 2.1	23.1 ± 0.6	22.8 ± 1.9	21.8 ± 2.2
Week 4-SPW	23.8 ± 0.8‡	24.0 ± 1.1‡	23.0 ± 1.5	22.1 ± 1.3
Baseline 1-SPS	21.8 ± 1.1	22.8 ± 0.4	22.2 ± 1.7	21.5 ± 1.8
Week 4-SPS	23.5 ± 0.6‡	23.0 ± 1.0	23.3 ± 1.2	21.7 ± 1.8

*Data are given as mean ± SD. NSAIDs indicates nonsteroidal anti-inflammatory drugs; SPW, self-paced walking test; SPS, self-paced stepping test; and $\dot{V}O_2$ max, maximum oxygen uptake.

†Placebo isotonic sodium chloride solution injection.

‡ $P < .05$ for within-groups comparison.

4 weeks after the SPW test, while only groups 1 to 3 reported less pain 4 weeks after the SPS test (**Table 4**). There were no differences among groups 1 to 3. At week 4, we observed significantly faster SPW exercise times and higher $\dot{V}O_2$ max in groups 1 and 2 and significantly faster SPS exercise times in group 1 (Table 4). At week 12, activity pain after the SS test was significantly ($P < .05$) lower in group 1, unchanged in group 2, and significantly ($P < .05$) higher in groups 3 and 4 compared with week 4 measures (Table 3). There were no significant differences among the 4 groups in SPW pain, exercise times, or $\dot{V}O_2$ max (Table 4) between weeks 4 and 12.

DEMOGRAPHIC AND CLINICAL OUTCOMES

There were no differences at baseline among demographic characteristics (Table 1). There were no differences in radiography scores among the groups at baseline and week 12 nor differences in $\dot{V}O_2$ max among the groups at baseline.

Range of motion (measured as the degrees of passive flexion of the study knee) was similar among all 4 groups at baseline. There was significant improvement in flexion in all 4 groups at week 4 and no differences among groups at weeks 4 and 12.

SUBGROUP ANALYSES

We performed post hoc analyses to examine whether differences among groups on the WOMAC subscale scores and the SPW and SPS test results were influenced by demographic or clinical characteristics (age, sex, BMI, radiography grade, and number of comorbidities). Similar significant ($P < .05$) effects on outcomes were seen among subgroups from groups 1 to 3. To determine if there was a dose response between compliance with the exercise program and effects on outcomes, we also examined the influence of percentage compliance on the WOMAC subscale scores. These analyses showed that there were no significant differences among the WOMAC

subscale scores for pain, functional performance, and stiffness with differing compliance. All groups showed high rates of compliance with this simple program.

COMMENT

This double-blind, placebo-controlled, randomized study provides support for the use of viscosupplementation with HA in the treatment of OA of the knee. With standard of care treatment (NSAIDs alone or with additives), pain at rest and following physical activity was reduced and physical functioning was improved compared with baseline measures. Moreover, the effect of hyaluronate sodium on activity-related pain and functional performance seems to improve with time from intervention compared with the effect of NSAIDs, which does not show continued improvement after 4 weeks of treatment.

Despite the increasing morbidity of pain and functional impairment, as well as the economic costs that ensue, standard therapies for OA have not progressed over the past few years even with the introduction of more selective anti-inflammatory medications.^{2,14,15} Standard therapies currently include the use of NSAIDs despite evidence of increased frequency and severity of adverse effects and associated morbidity, particularly in elderly patients.^{16,17} Exercise is also suggested as standard treatment; however, adoption rates are disappointingly low.^{18,19} Further, no consistent long-term improvement of physical function with the use of NSAIDs has been reported.^{20,21} LaMontagna et al²² found that improvement in daily living activities with 2 different NSAIDs was limited to the first few weeks of treatment, then falling to baseline levels. Critics even suggest that the removal of objective pain sensation may lead to increased rates of cartilage deterioration with long-term NSAID use²¹ and lead to further pain and functional decline. Certainly, new therapies are desirable, including intra-articular hyaluronate sodium therapy²³⁻²⁵ and the better promotion of exercise therapy,¹⁹ both of which address underlying patho-

physiologic conditions, improve symptoms, and are relatively free of adverse events.

The literature lacks substantial investigation comparing HA with placebo and other standard OA therapies.²⁶ A few studies^{24,27,28} have systematically investigated the effect of HA and found variable effects on pain control, and none to our knowledge have investigated the effect on physical functioning. In contrast, dose-finding studies have shown impressive improvement in pain control after 3 injections of HA in up to 82% of patients at 26 weeks²⁹⁻³¹ with a low adverse event profile.³²

The mechanism of action of intra-articular HA injection has not been determined. Removal of water-soluble mediators of inflammation and articular breakdown products could explain the therapeutic effect in part.³ However, Dawes et al³³ found that tidal irrigation of the knee conferred no long-term benefit over saline injection. Instead, there is support for HA restoration of the rheological (including the complex interaction of flow and deformation of the articular matrix during the loading and unloading of the joint) properties of the osteoarthritic joint. Hyaluronic acid is a large molecular component of the articular matrix that acts as a "lubricant" when movements are slow (viscous properties) and as a "shock absorber" when movements are fast (elastic).³⁴ There also seems to be free radical scavenger activity of HA.³⁵ If the OA knee joint is characterized by lower HA concentration and molecular weight, reduced elastoviscosity has been hypothesized to lead to reduced joint stability during loading, resulting in pain and reduced function.³⁵ Hence, it has been hypothesized that supplementation of the OA articular matrix with exogenous HA may restore the joint environment to a level of greater function and less pain.

Although the therapeutic effect on pain relief may be lost after several months because of finite residence time (between 8 and 16 months³⁵), HA can be readministered with no apparent adverse effects. However, the efficacy for pain and functional improvement at an optimal dosing regimen has not been described.³¹ Therefore, further investigation of the impact of HA differing in molecular weight, concentration, dosing intervals, and number of injections on functional outcomes are needed.

The significant improvement in pain and physical functioning from baseline among all groups, including control group 4, could be attributed to the concomitant introduction of a simple resistive exercise program.¹³ The low rate of adverse events and high rate of exercise compliance in group 4 suggests and supports the recommendations^{18,20} that a combination of exercise and other medical therapy should be considered for most patients with OA. Presently, low levels of activity among this population suggest that there is room for low-intensity exercise therapy. However, modest effects of exercise on pain, disability, and physical functioning support our observation.³⁶ We chose functional tasks within the clinical range of patients with knee OA as key outcomes.¹³ Certainly, self-selection of functional tasks (ie, walking and stair climbing or stepping) help define the level of functional independence and is useful in determining the effectiveness of therapeutic interventions in this population. Marks³⁷ observed that reporting of joint pain in

patients with knee OA was correlated most with stair climbing rather than other observations, including BMI or disease severity. Thus, we believe these functional measures are important determinants of therapeutic intervention in this study and should be used in future efficacy studies in OA.

In summary, intra-articular hyaluronate sodium therapy was similar to NSAID therapy in improving pain at rest, while the introduction of a simple exercise program improved functional performance in all 4 groups compared with baseline measures. It seems that hyaluronate sodium therapy may show greater efficacy for activity-related pain and improve functional performance more than NSAID or exercise therapy alone. Future studies regarding optimal dosing, concentration, and the long-term impact of hyaluronate sodium on OA in the knee and other weight-bearing joints are needed.

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Corresponding author and reprints: Robert J. Petrella, MD, PhD, Centre for Activity and Ageing, University of Western Ontario, 1490 Richmond St N, London, Ontario, Canada N6G 2M3.

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