CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 385, pp. 130–143

Efficacy and Safety of Intraarticular Sodium Hyaluronate in Knee Osteoarthritis

Kenneth D. Brandt, MD; Joel A. Block, MD**; Joseph P. Michalski, MD†; Larry W. Moreland, MD‡; Jacques R. Caldwell, MD§; Philip T. Lavin, PhD‖; and the ORTHOVISC® Study Group*

A prospective, multicenter, randomized, double-blind, controlled trial was conducted in 226 patients with knee osteoarthritis to evaluate the safety and efficacy of intraarticular injections of sodium hyaluronate. Patients were randomized to three weekly injections of 30 mg sodium hyaluronate or physiologic saline (control) and were observed for an additional 25 weeks. In comparison with the control group, among patients who completed at least 15 weeks of the study and whose Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was less than 12 at baseline, sodium hyaluronate injection resulted in improvement in Western Ontario and McMaster Universities Osteoarthritis Index pain score, patient and investigator global assessments, and pain on standing from Weeks 7 to 27. Fifty-eight percent of patients treated with sodium hyaluronate achieved a 5-unit or greater improvement in mean pain score from Weeks 7 through 27, compared with 40% of control patients. In addition, nearly twice as many patients treated with sodium hyaluronate as with saline (30% versus 17%, respectively) achieved a net improvement of at least 7 units. In contrast to treatment with saline, Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was inversely related to the magnitude of improvement after treatment with sodium hyaluronate. Few side effects were attributed to treatment, and no differences between treatment groups were seen in this respect (sodium hyaluronate, nine [8%]; saline, 11 [10%]). The incidence of injection site reactions was low (sodium hyaluronate, 1.2%; saline, 1.5%). The results indicate that sodium hyaluronate treatment is well tolerated and produces statistically and clinically significant improvement of symptoms in patients with mild to moderate knee osteoarthritis in whom pain in the contralateral knee is relatively modest.

From the *Indiana University School of Medicine, Indianapolis, IN; the **Rush-Presbyterian-St Luke's Medical Center, Chicago, IL; †University of South Alabama, Mobile, AL; ‡University of Alabama at Birmingham, Birmingham, AL; §Halifax Clinical Research Institute, Daytona Beach, FL; and ‖Boston Biostatistics, Inc, Framingham, MA.

Supported in part by a grant from Anika Therapeutics, Inc, Woburn, MA.

Reprint requests to Kenneth D. Brandt, MD, Rheumatology Division, Indiana University School of Medicine, 541 Clinical Drive, Room 492, Indianapolis, IN 46202–5103.

Received: November 24, 1999.

Revised: June 20, 2000; August 7, 2000.

Accepted: September 6, 2000.

Osteoarthritis is the most prevalent joint disease in older adults and is characterized by deterio-

ration and loss of articular cartilage, subchondral sclerosis, and osteophyte formation. Approximately 15.8 million Americans between the ages of 25 and 74 years (12% of the population in this age range) are afflicted with osteoarthritis, and these numbers are expected to increase markedly as the proportion of elderly people in the population increases.[12,20,28] Although several options are available for treatment of osteoarthritis symptoms—simple analgesics, nonsteroidal antiinflammatory drugs, intraarticular injection of glucocorticoids, and hyaluronic acid preparations—no medical intervention has been shown to halt disease progression or reverse joint damage in humans.[23]

First used in the 1970s for cataract surgery and later for other ophthalmologic surgery, hyaluronic acid preparations have been investigated intensively as an intraarticular treatment for symptoms of knee osteoarthritis. Hyaluronic acid is an important component of synovial fluid and normal cartilage and is thought by some to protect the articular cartilage and soft tissue surfaces of the knee by acting as a lubricant and imparting viscoelastic properties to the joint because of its high viscosity.[5] The concentration of hyaluronic acid in the synovial fluid of patients with knee osteoarthritis is lower than that of normal synovial fluid.[5,7] Intraarticular hyaluronic acid treatment has been proposed as a means of relieving symptoms, improving joint function, and potentially halting deterioration of the joint, although others have raised doubt that viscosupplementation accounts for the beneficial effects observed in some patients after intraarticular injection of hyaluronic acid.[10] The objectives of the current study were to assess the safety and efficacy of the sodium hyaluronate formulation ORTHOVISC® (30 mg sodium hyaluronate; Anika Therapeutics, Inc, Woburn, MA) for treatment of joint pain in patients with idiopathic osteoarthritis of the knee.

MATERIALS AND METHODS

Patients

Patient eligibility was evaluated during a screening visit approximately 2 weeks before study entry. Patients enrolled in the study were older than 50 years, willing to discontinue all analgesics and nonsteroidal antiinflammatory drugs in a washout period equivalent to five half-lives of the relevant drug preceding entry into the study, able to walk 50 feet unassisted, and not pregnant or planning a pregnancy. All patients had idiopathic osteoarthritis according to American College of Rheumatology criteria,[3] Kellgren-Lawrence Grade II or III radiographic evidence of knee osteoarthritis,[20] and a summed Western Ontario and McMaster Universities Osteoarthritis Index[8] pain score of 13 or greater (possible range, 5–25) in the index (treated) knee and less than 13 in the contralateral (untreated) knee. All patients were required to provide written informed consent.

Exclusion criteria included initiation of a quadriceps exercise program within 4 months of screening; oral or intramuscular steroid use within 2 months of screening; intraarticular injection of hyaluronic acid within the past 12 months; Kellgren-Lawrence Grade IV radiographic changes in either knee; treatment with anticoagulants, immunosuppressives, or muscle relaxants; inability to tolerate acetaminophen; clinically significant comorbidity (renal or hepatic disease) or abnormality in routine laboratory tests; or allergy to lidocaine. None of the patients had previously undergone knee arthroplasty.

Patients who were discontinued from the study were analyzed for treatment related differences. Major protocol violations included surgery, therapy for a new condition, initiation of a new physical therapy regimen, and use of prescribed medications. Patients were considered to be noncompliant when they missed a visit.

Study Design

A prospective, multicenter, randomized, double-blind, parallel-group, saline-controlled study was conducted at 10 sites in the United States between May 1996 and June 1997. The study was conducted under an Investigational Device Exemption and was approved by the institutional review board of each participating institution.

Study materials were prepackaged to mask treatment identity, and patients were randomized 1:1 to one of two treatment groups: a sodium hyaluronate group or a saline control group. To ensure treatment blinding, each study site was required to have an injecting physician, a masked observer, and an adverse event monitor. The masked

observer did all study assessments. In the sodium hyaluronate group, 2 mL (15 mg/mL) of ORTHOVISC, a high molecular weight (1.0 to 2.9 million Da)[6] hyaluronan purified from rooster combs and manufactured under current good manufacturing process standards,[34] was administered by intraarticular injection. Patients received three injections, separated by 1-week intervals. In the saline control group, three intraarticular injections of 2 mL saline were administered similarly during a 2-week period. In both treatment groups, the intraarticular injections were done after the skin and subcutaneous tissue had been anesthetized with 3 to 5 mL of a 1% lidocaine HCl solution. Only the index knee was treated. Patients were followed up for 25 weeks after the last injection (total study duration of 27 weeks).

Patient Monitoring

At the screening visit, the radiographic eligibility of the patient was ascertained; a physical examination of both knees was done including measurement of range of motion, circumference, and assessment of effusion (present or absent); the patient's vital signs were recorded; and standard laboratory tests (complete blood count, serum chemistries, urinalysis) were done. During screening, candidates for the study completed a Western Ontario and McMaster Universities Osteoarthritis Index questionnaire that assessed the level of pain, stiffness, and functional impairment in each knee separately. Before enrollment, patients were required to discontinue use of all analgesics or nonsteroidal antiinflammatory drugs or both for an interval equivalent to five half-lives of the drug. The Western Ontario and McMaster Universities Osteoarthritis Index questionnaire was completed at screening and at Weeks 0, 1, 2, 3, 7, 11, 15, 21, and 27. Index knee pain after a 50-foot walk also was assessed (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = extreme) at Weeks 0, 1, 2, 3, 7, 11, 15, 21, and 27. Acetaminophen (to a maximum of 4 g daily) was the only pain medication permitted in the 2 weeks preceding entry into the study and during the 27-week study period. No acetaminophen use was permitted for at least 24 hours before each treatment or followup visit.

The study protocol required 10 patient visits, including the screening visit. Potential candidates returned for a baseline visit after washout (Week 0), at which time candidates who met the enrollment criteria received the first of the series of intraarticular injections. Patients then returned for additional knee injections at Weeks 1 and 2 and for subsequent evaluations at Weeks 3, 7, 11, 15, 21, and 27. All study sites were monitored for good clinical practices by an independent contract research organization.[17]

The safety of treatment was determined from adverse event reports, records of vital signs, and measurement of clinical laboratory parameters.

Statistical Methods

Intent to Treat and Safety Analyses

The results of treatment were assessed during each patient visit. In the intent to treat analysis, the study was designed to have 80% power to detect a 0.5-unit difference between the two treatment groups with respect to the summed Western Ontario and McMaster Universities Osteoarthritis Index scores for each of the end points, with 5% Type I error in two-sided hypothesis tests. All individual Western Ontario and McMaster Universities Osteoarthritis Index pain 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 Western Ontario and McMaster Universities Osteoarthritis Index pain score is 5 to 25, whereas the possible range for the stiffness score and function score are 2 to 10 and 17 to 85, respectively.[9] In addition to the Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and function scores, treatment outcome measures included patient and investigator global assessment; pain on standing; pain after a 50-foot walk; and time to walk 50 feet. A clinically meaningful improvement, relative to the baseline pain score, was defined as a decrease of at least three units.

All patients who received at least one intraarticular injection were included in the intent to treat and safety analyses. Adverse events were monitored continuously throughout the 27-week trial and were categorized by frequency, severity, body system, treatment group, and relationship to study device, as judged by the investigator. The MedDRA 1.5 coding system (MedDRA™, version 1.5. AutoCode CS, TRW Inc, Lyndhurst, OH) was used to classify adverse events.

Post Hoc Analysis

In addition to the analyses of the intent to treat population, analyses were done on patients who completed a minimum of 15 weeks of the study, had no

major protocol violations, and in whom the Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was lower than 12 (in contrast to the study entry requirement of lower than 13). This effectiveness population was used as control for the severity of symptoms in the contralateral knee, and these analyses were done based on the finding in the intent to treat analysis that a Western Ontario and McMaster Universities Osteoarthritis Index pain score of 12 or greater for the contralateral knee appeared to mitigate the effect of treatment of the index knee. Change from baseline within treatment groups was assessed using sign tests, whereas between treatment group differences were assessed using Wilcoxon rank sum tests. Analysis of variance with repeated measures was applied to the efficacy data from followup visits at Weeks 7 through 27. Tests for treatment by contralateral knee pain interaction were done to identify and confirm the findings. No adjustments were made for repeated significance tests involving multiple end points in different populations. Statistical significance for all comparisons was set at $p < 0.05$.

RESULTS

Patient Demographics and Baseline Disease Characteristics

Intent to Treat Population

The 226 patients who received at least one intraarticular injection constituted the intent to treat population. The demographic and baseline disease characteristics of this cohort are shown in Table 1. Except for body mass index, which was higher in the sodium hyaluronate group than in the saline control group, there were no differences between the two treatment

TABLE 1. Patient Demographics and Baseline Disease Characteristics

	Intent to Treat Population		Effectiveness Population*	
Parameter	*Na-HA (n = 114)*	*Saline (n = 112)*	*Na-HA (n = 66)*	*Saline (n = 69)*
Age, mean years ± SD	65 ± 8.4†	67 ± 8.4	65 ± 8.2	67 ± 8.4
Gender, number of subjects (%)				
Male	42 (37)	41 (37)	26 (39)	26 (38)
Female	72 (63)	71 (63)	40 (61)	43 (62)
Race, number of subjects (%)				
White	85 (75)	80 (71)	50 (76)	49 (71)
Black	20 (18)	23 (21)	10 (15)	18 (26)
Other	9 (8)	9 (8)	6 (9)	2 (3)
Body mass index, kg/m^2	32.0 ± 6.0†	30.1 ± 6.2	31.8 ± 6.7	29.8 ± 6.5
Bilateral knee OA, number of subjects (%)‡	89 (78)	99 (88)	50 (76)	60 (87)
Analgesic/NSAID use, number of subjects (%)	62 (54)	69 (62)	37 (56)	36 (52)
WOMAC pain score, mean ± SD				
Index knee	16.4 ± 2.8	16.3 ± 2.7	16.1 ± 2.5	15.8 ± 2.9
Contralateral knee	9.3 ± 2.6	9.6 ± 2.6	8.5 ± 2.2	8.5 ± 2.1
WOMAC stiffness score, mean ± SD				
Index knee	7.0 ± 1.5	6.8 ± 1.8	6.8 ± 1.6	6.7 ± 1.7
WOMAC function score, mean ± SD				
Index knee	54.8 ± 10.6	54.5 ± 11.3	53.9 ± 10.5	3.5 ± 11.1
Index knee pain after 50 foot walk	—	—	1.9 ± 1.0	2.0 ± 1.0

Na-HA = sodium hyaluronate; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; OA = osteoarthritis; NSAID = nonsteroidal antiinflammatory drug.

*Defined as patients who completed at least 15 weeks of study without any major protocol violations and whose WOMAC pain score was less than 12 in the contralateral knee at baseline.

‡Indicates significant difference ($p \leq 0.05$) from control.

‡Based on physical examination and radiographic evidence (Kellgren-Lawrence Grade II or III).

groups with respect to demographic or baseline disease parameters. A majority (> 78%) of patients in each treatment group had radiographic evidence of osteoarthritis in both knees.

At baseline, the summed Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and function scores; patient and investigator global assessments; and scores for pain on standing and pain after a 50-foot walk for the index knee in the two treatment groups were comparable (Table 1). The mean (± standard deviation) Western Ontario and McMaster Universities Osteoarthritis Index pain scores for the contralateral knee were 9.3 ± 2.6 and 9.6 ± 2.6 in the sodium hyaluronate and saline control groups, respectively ($p = 0.78$). Use of nonsteroidal antiinflammatory drugs or acetaminophen, or both, for knee pain at the time of enrollment was low in both groups (54% in the sodium hyaluronate group; 62% in the saline control group).

Discontinuation of Treatment

In the intent to treat population, 91 patients in the sodium hyaluronate group (80%) and 84 in the saline control group (75%) completed the 27-week study (Fig 1). The most frequent cause of discontinuation was worsening of knee pain, which occurred in 11% of patients treated with sodium hyaluronate and 13% of patients who received saline injections. Ten patients were lost to followup, and four patients were terminated from the study because of noncompliance. No significant differences existed between treatment groups with respect to reasons for discontinuation.

Effectiveness Population

The effectiveness population consisted of 135 patients (66 patients in the sodium hyaluronate group and 69 patients in the saline control group) who completed at least 15 weeks of the protocol without major violations and whose Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was less than 12 at baseline (Table 1). No clinically meaningful between group differences were apparent in the effectiveness population with respect to any demographic parameters or baseline disease characteristics, although body mass index was marginally higher in patients randomized to the sodium hyaluronate treatment ($p = 0.06$) group than in those in the saline control group.

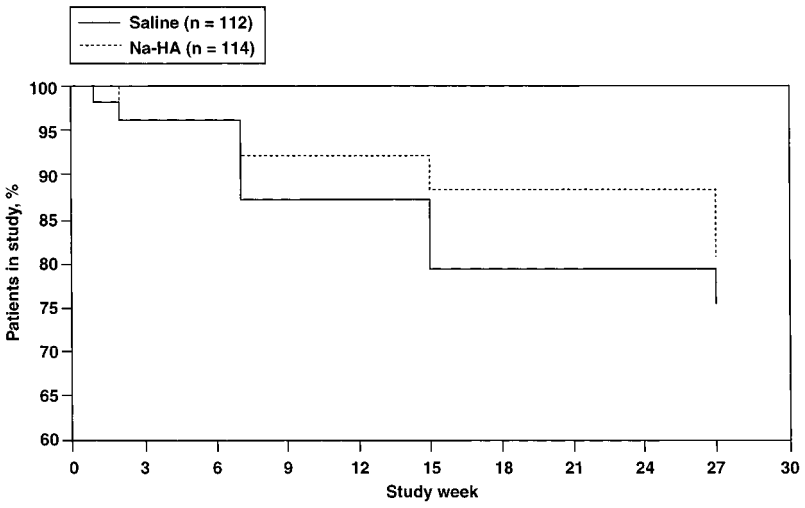

Fig 1. Kaplan-Meier curve showing the onstudy progress of patients treated with saline and patients treated with sodium hyaluronate (Na-HA). Data in the graph represent the intent to treat population.

Mean Western Ontario and McMaster Universities Osteoarthritis Index pain scores for the index knee at baseline were comparable in the two treatment groups (16.1 ± 2.5 in the sodium hyaluronate group and 15.8 ± 2.9 in the saline control group). Baseline mean Western Ontario and McMaster Universities Osteoarthritis Index pain scores for the contralateral knee also were comparable in the two treatment groups, and approximately one point lower than those observed in the intent to treat population (8.5 and 9.5, respectively). Values for the timed 50-foot walk in the two treatment groups also were comparable ($p > 0.05$) (Table 1).

Effect of Sodium Hyaluronate on Knee Pain, Stiffness, and Function

Intent to Treat Population

For all end points, sodium hyaluronate and saline injections resulted in significant improvement from the baseline scores. Although trends for all outcome measures favored sodium hyaluronate over the saline control at all times beyond 3 weeks, differences between the treatment groups did not reach statistical significance.

Mean daily acetaminophen use during the study for the sodium hyaluronate group and saline control group was comparable (1435 ± 1445 mg and 1670 ± 1615 mg, respectively; $p = 0.123$).

Effectiveness Population

Change from baseline scores for Western Ontario and McMaster Universities Osteoarthritis Index outcome measures in this subgroup are shown in Table 2 and Figure 2. For all end points, sodium hyaluronate and saline injections resulted in significant improvement. Although statistically significant differences between groups were not seen at all times and for all assessments, improvement in Western Ontario and McMaster Universities Osteoarthritis Index pain score favored patients receiving sodium hyaluronate at all times. For Western Ontario and McMaster Universities Osteoarthritis Index pain, sodium hyaluronate was

TABLE 2. Treatment Outcomes: Change From Baseline (Effectiveness Population)

End Point	Treatment Group	Number of Patients	Baseline	Mean Decrease From Baseline*							
				Week 1	*Week 2*	*Week 3*	*Week 7*	*Week 11*	*Week 15*	*Week 21*	*Week 27*
WOMAC	Na-HA	66	6.8 ± 1.6	−1.0	−1.1	−1.5	−1.7	−1.9†	−1.8	−1.8	−1.7
Stiffness score	Saline	69	6.7 ± 1.7	−0.9	−1.2	−1.5	−1.5	−1.2	−1.4	−1.2	−1.1
WOMAC	Na-Ha	66	53.9 ± 10.5	−7.1	−8.7	−11.4	−15.0	−15.0†	−14.0	−14.4	−14.7
Function score	Saline	69	53.5 ± 11.1	−5.1	−8.6	−10.0	−11.3	−10.5	−11.5	−11.3	−9.8
Time to walk	Na-HA	66	24.0 ± 14.6	−1.0	−1.2	−1.8	−2.0	−2.1†	−1.8	−2.2†	−2.0
50 feet, seconds	Saline	69	23.9 ± 14.9	−0.6	−1.6	−1.7	−1.4	−1.0	−1.2	−0.7	−0.6

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; Na-HA = Sodium hyaluronate.

*Negative changes from baseline represent improvement.

†Indicates statistically significant difference between treatment groups, $p < 0.05$.

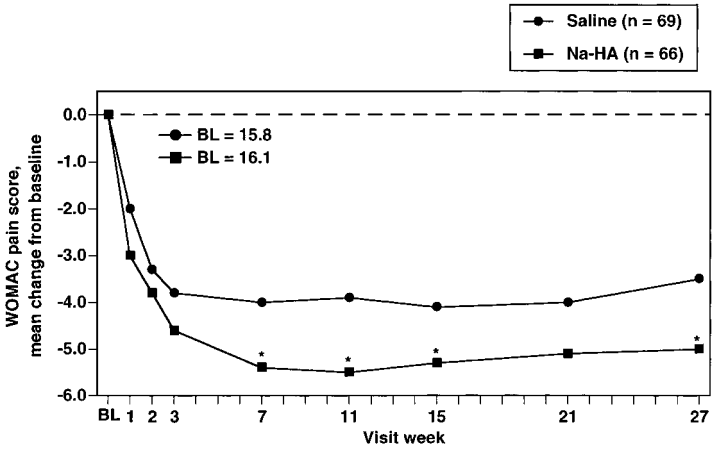

Fig 2. Mean change from baseline in Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score in patients with contralateral WOMAC knee pain score less than 12 (effectiveness population) treated with saline and in patients treated with sodium hyaluronate (Na-HA). Pain was assessed at baseline (BL) and at Weeks 1, 2, 3, 7, 11, 15, 21, and 27. Asterisks indicate significant difference between treatment groups ($p < 0.05$), as determined by analysis of variance with repeated measures. BL = baseline.

significantly more effective than saline at Weeks 7, 11, 15, and 27 (Fig 2). In addition, only 8% of patients treated with sodium hyaluronate, but 13% of patients treated with saline, reported worsening of Western Ontario and McMaster Universities Osteoarthritis Index pain. A significant benefit of sodium hyaluronate versus saline also was observed for index knee stiffness ($p = 0.03$) and function ($p = 0.04$) at Week 11 and for 50-foot walk time at Weeks 11 ($p = 0.04$) and 21 ($p = 0.04$).

The magnitude of improvement in the summed Western Ontario and McMaster Universities Osteoarthritis Index pain score for the index knee, relative to the baseline value, also was examined (Table 3). Fifty-eight percent of patients treated with sodium hyaluronate achieved a net improvement of 5 units or greater (approximately 50% improvement from their baseline value) in their pain score from Weeks 7 through 27, whereas only 40% of control patients achieved equivalent improvement ($p = 0.04$). Nearly twice as many patients treated with sodium hyaluronate as those who received saline achieved a net improvement of 7 units or greater (30% versus 17%, respectively; $p > 0.05$).

Results of patient global assessments, investigator global assessments, and pain on standing are shown in Figure 3. Mean patient global assessment scores in the two treatment groups were similar at baseline (2.2 ± 0.8). Likewise, there was no between group difference in the scores for either the investigator global assessment (mean, 2.1 ± 0.7 for sodium hyaluronate, 2.0 ± 0.7 for control) or pain on standing (mean, 2.0 ± 1.0 for sodium hyaluronate, 1.9 ± 0.9 for control) at baseline.

For all three of the end points mentioned, sodium hyaluronate and saline injections resulted in significant improvements across Weeks 7 through 27. Sodium hyaluronate was more effective than saline at Week 11 ($p = 0.006$) and Week 21 ($p = 0.03$) in the patient

TABLE 3. Categoric Improvement From Baseline in WOMAC Pain Score* for Index Knee: Effectiveness Population

	Percent of Patients	
Improvement	*Na-HA (n = 66)*	*Saline (n = 69)*
≥ 0 units	92	87
≥ 2.5 units	83	67
≥5.0 units	58†	40
≥ 7.0 units	30	17

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; Na-HA = Sodium hyaluronate.

*Change from baseline WOMAC pain score was the mean of WOMAC pain from Weeks 7 to 27.

†$p = 0.04$.

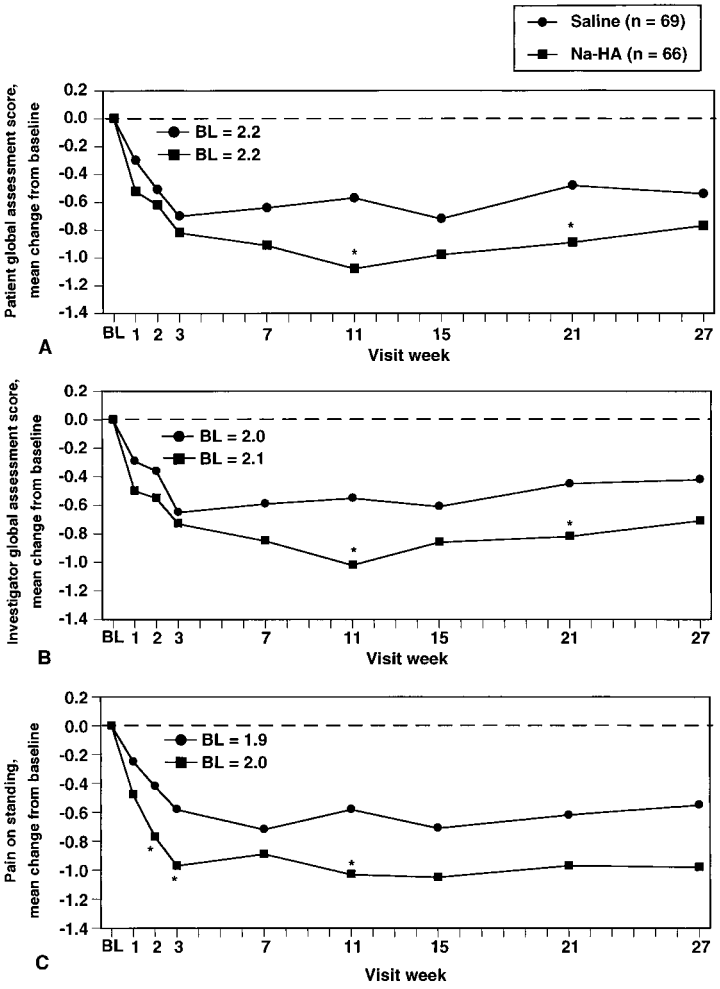

Fig 3A–C. Mean change from baseline for (A) patient global assessment score, (B) investigator global assessment score, and (C) pain on standing in patients with contralateral Western Ontario and McMaster University Osteoarthritis Index (WOMAC) knee pain score less than 12 (effectiveness population) treated with saline and in patients treated with sodium hyaluronate (Na-HA). Patient and investigator global assessments and pain on standing assessments were made at baseline (BL) and at Weeks 1, 2, 3, 7, 11, 15, 21, and 27. Asterisks indicate significant difference between treatment groups ($p < 0.05$), as determined by analysis of variance with repeated measures.

global assessment and at Week 11 ($p = 0.01$) and Week 21 ($p = 0.04$) in the investigator global assessment (Fig 3). Separation of scores between treatment groups for the patient and physician global assessments began by Week 3, attained statistical significance by Week 11, and was sustained through Week 27, although the differences between the treatment groups were not statistically significant at all points. Significant differences favoring sodium hyaluronate over the saline control were observed in pain on standing at Week 11 ($p = 0.02$) and Week 27 ($p = 0.02$) (Fig 3C). Although statistically significant advantages of sodium hyaluronate over saline were not observed at all times, a numerical advantage of sodium hyaluronate over saline was observed for all end points at all times evaluated.

In both treatment groups, the mean daily consumption of acetaminophen throughout the duration of the study was lower than that in the intent to treat population (sodium hyaluronate, 1050 ± 920 mg; saline, 1300 ± 1040 mg), although the difference was not statistically significant.

Contralateral Knee Pain and Treatment Efficacy

In both treatment groups, contralateral knee pain persisted from baseline to the end of the

TABLE 4. Relationship Between Contralateral Knee Pain and Treatment Outcome in the Index Knee

WOMAC Pain in Untreated Knees	Number of Patients		Number of Visits*		
	Na-HA	*Saline*	*Patient Global*	*Investigator Global*	*Pain on Standing*
< 13 (per protocol)	93	88	0	0	0
< 12	66	69	2	2	2
< 11	48	55	2	2	2
< 10	38	37	4	2	3

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; Na-HA = Sodium hyaluronate.

*Number of visits at which statistically significant ($p \leq 0.05$ by Wilcoxon rank-sum test) differences between treatment groups were observed during the evaluations at Weeks 7, 11, 15, 21, and 27.

study (Week 27). No improvement in contralateral knee pain was associated with treatment of the index knee. Although the mean Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee tended to be higher at Week 27 than at baseline (sodium hyaluronate, 10.4 versus 9.5; saline, 9.9 versus 9.3, respectively), in neither group was the increase statistically significant.

In the intent to treat population, the level of pain in the contralateral knee affected the efficacy of treatment of the index knee (Table 4). When all patients with a Western Ontario and McMaster Universities Osteoarthritis Index pain score less than 13 for the contralateral knee were included in the analyses, no consistent statistical advantage of treatment with sodium hyaluronate in comparison with saline was apparent. In contrast to treatment with saline, it was apparent that the Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was inversely related to the magnitude of improvement after treatment with sodium hyaluronate (the efficacy of sodium hyaluronate treatment of the index knee increased as the level of pain in the contralateral knee decreased).

Safety Profile of Sodium Hyaluronate

All patients were included in the safety analyses. The adverse event profiles for the two treatment groups are shown in Table 5. Seventy-six patients in the sodium hyaluronate group (67%) and 74 patients in the saline control group (66%) reported 225 and 228 adverse events, respectively. In both groups, the most common adverse event reported was arthralgia (64 events in 49 patients). In 31 (48%) of those cases, arthralgia was associated with a joint other than the knee. In the other 33 instances, arthralgia was reported in the contralateral knee by 23 patients, in the index knee by seven patients, and in both knees by two patients (knee not designated for one subject). In only three instances (in three patients) was arthralgia considered by the investigator

TABLE 5. Adverse Events Reported by 5% or More of Patients (by Body System): Intent to Treat Population

Adverse Event*	Patients, Number (%)	
	Na-HA (n = 114)	*Saline (n = 112)*
Musculoskeletal	34 (30)	30 (27)
Respiratory	26 (23)	18 (16)
General body	21 (18)	23 (21)
Nervous system	15 (13)	16 (14)
Gastrointestinal	11 (10)	16 (14)
Urinary	6 (5)	9 (8)
Skin	5 (4)	6 (5)

Na-HA = Sodium hyaluronate.

*No significant differences ($p > 0.05$) between the two groups were found by Fisher's exact test.

to be related to treatment (sodium hyaluronate in one patient, saline in two patients). No between group differences were observed with respect to vital signs or laboratory test results.

Nine patients treated with sodium hyaluronate (8%) and 11 patients treated with saline (10%) reported 32 adverse events that were attributed to treatment. The most common adverse events included injection site reactions, such as pain, local inflammation, or ecchymosis (n = 12); musculoskeletal events, such as arthralgia or worsening arthritis (n = 7); gastrointestinal events, such as nausea, diarrhea, dyspepsia, and abdominal pain (n = 6); and general fatigue and pain (n = 3). No differences between the two treatment groups with respect to the nature of the adverse events were evident.

A significant proportion of treatment related adverse events (nine events in five patients) were associated with the injection and involved a superficial localized inflammatory reaction or pain at the injection site. Only one patient reported severe injection site pain; all other injection site events were considered mild or moderate. No patient had acute synovitis develop or underwent arthrocentesis for effusion after injection. All injection-related adverse events were of brief duration and resolved promptly after local application of an ice pack or the use of acetaminophen, or both, as permitted by the study protocol. The overall incidence of injection site reactions was 1.2% for sodium hyaluronate and 1.5% for saline injections.

Serious adverse events were reported by six patients treated with sodium hyaluronate (5%) and four patients (4%) who received saline. These adverse events included diverticulitis, esophagitis, cholecystitis, hyperglycemia, atrial fibrillation, congestive heart failure, deep vein thrombosis, pneumonia, asthma, congenital hernia, prostatic disorder, and carcinoma. Only cholecystitis was reported by more than one patient (n = 2). None of the serious adverse events was thought by the investigator to have been related to treatment. All 10 patients who reported serious adverse events had received all three intraarticular injections, were followed up for 25 weeks after the final injection, and experienced no additional complications. No patient died during the study.

DISCUSSION

For symptomatic treatment of osteoarthritis of the knee, therapeutic options other than nonsteroidal antiinflammatory drugs may benefit patients by decreasing the morbidity associated with the latter. One promising approach to long-term osteoarthritis therapy involves the intraarticular injection of hyaluronic acid. The safety and efficacy of several hyaluronic acid formulations have been investigated in patients with osteoarthritis of the knee.[2,4,15,16,18,21,24–27,35,36] Two hyaluronic acid products recently have been introduced in the United States for treatment of osteoarthritis of the knee in patients in whom conservative nonpharmacologic therapy (exercise program, weight loss) and pharmacologic therapy with simple analgesics, such as acetaminophen, have failed. Hylan G-F 20 (Synvisc®, Biomatrix, Inc, Ridgefield, NJ) is a high molecular weight (6 million Da),[6] divinylsulfone-crosslinked hylan that has shown safety and efficacy in treatment of osteoarthritis of the knee.[1,2,26,35] Hyalgan (Fidia, Padua, Italy) is a natural hyaluronic acid whose ability to reduce knee pain in osteoarthritis also has been documented.[4,16,24,31] Both provide durable pain relief, suggesting this class of agents may represent a safe and efficacious alternative to nonsteroidal antiinflammatory drugs and intraarticular steroid injections.

The sodium hyaluronate formulation used in the current study is a natural material extracted from rooster combs. It is a purified, high molecular weight, high concentrated, noncrosslinked, stable hyaluronic acid preparation. The preparation consists of 2 mL of a sterile, nonpyrogenic, clear, viscoelastic solution of sodium hyaluronate (30 mg) contained in a single use syringe. It possesses a higher molecular weight (1.0–2.9 million Da versus 0.6 million Da, respectively) and hyaluronate concentration (15 mg/mL versus 10 mg/mL,

respectively) than does Hyalgan.[32] In addition, the hyaluronate is injected in three doses (as is Synvisc), in contrast to the five injections required for Hyalgan. Because the role of intraarticular sodium hyaluronate for treatment of moderately severe osteoarthritis of the knee has not been well established in the United States, the authors sought to investigate the efficacy and safety of this formulation in a multicenter clinical trial.

The demographic and disease characteristics of the study population were typical of those of patients with idiopathic osteoarthritis of the knee; the study subjects had a higher body mass index (31) than the population norm, and most of the patients (63%) were female. The severity of disease was considered moderate, based on the Kellgren-Lawrence grade and Western Ontario and McMaster Universities Osteoarthritis Index pain score, and with the exception of body mass index, no other imbalances existed between the treatment groups with respect to baseline characteristics. The relatively low proportion of patients who were taking nonsteroidal antiinflammatory drugs or acetaminophen at the time of entry into the study (Table 1) was attributed, for the most part, to lack of efficacy or to adverse events experienced during prior use of these agents. Scholes et al[30] found that only 15% of patients with osteoarthritis of the knee for whom a nonsteroidal antiinflammatory drug was prescribed still were taking the same drug 12 months later.

In the efficacy population, statistically significant advantages of sodium hyaluronate treatment, relative to the saline control, were observed in the patient and investigator global assessments and in pain on standing from Weeks 11 to 27. In addition, significant differences from baseline, favoring sodium hyaluronate, were observed for all treatment outcomes during one or more visits. In other studies, comparable results were reported in the intent to treat population by investigators in European centers who evaluated the role of this intraarticular sodium hyaluronate in osteoarthritis of the knee.[19,33]

In the effectiveness population, significant differences in Western Ontario and McMaster Universities Osteoarthritis Index scores were observed between treatment groups throughout the study. In this subgroup, sodium hyaluronate ameliorated knee pain and stiffness and improved function and mobility (time to walk 50 feet). In addition, alleviation of pain persisted for the entire duration of the study. The 6-month durability of symptom relief after intraarticular sodium hyaluronate injection occurred despite rapid clearance (24 to 48 hours) of radiolabeled sodium hyaluronate from the joint.[22] After the series of three injections, the symptom relief advantage of sodium hyaluronate at Week 27 was consistent with the durability of pain relief reported with other hyaluronic acid formulations.[2,14–16,18,21,27,35]

Although significant long-term benefit was observed in the subgroup of patients with contralateral Western Ontario and McMaster Universities Osteoarthritis Index knee pain less than 12 who received intraarticular sodium hyaluronate injection, little improvement, relative to the saline control group, was observed in the intent to treat population. Because of the mitigating influence of contralateral knee pain on efficacy of treatment of the index knee, only patients with a Western Ontario and McMaster Universities Osteoarthritis Index pain score less than 12 for the contralateral knee were included in the effectiveness analysis. The authors are aware of no previous clinical trials of intraarticular hyaluronic acid (or nonsteroidal antiinflammatory drugs or analgesics) that have examined outcomes in the index knee in relation to the severity of pain in the contralateral knee. Creamer et al[11] found that when patients with bilateral symptomatic osteoarthritis of the knee received a placebo or intraarticular bupivacaine injection into the more painful knee, the pain score for that knee decreased, suggesting that pain originates from nerve endings within or close to the joint lining. However, pain in the contralateral knee also diminished in that study, although less strikingly than in the index knee. Although biomechanical studies were not done as part of

the current clinical trial or in the study by Creamer et al,[11] it is reasonable to hypothesize that patients in whom contralateral knee pain is more severe place a disproportionate load on the index knee, in comparison with patients who have less pain in the contralateral knee. In the current study, this may have mitigated the analgesic effect of sodium hyaluronate injections in the former group.

In addition, moderate to severe contralateral knee pain may mask the robustness of the pain response in the index knee after sodium hyaluronate treatment, especially when study end points require the patient to assess overall measures (global scores and time to walk 50 feet), rather than knee specific outcomes. Disease specific and joint specific assessments are needed to fully evaluate the effect of treatment of osteoarthritis of the knee. This has important implications for measurement of a treatment benefit in patients with moderately severe osteoarthritis of the knee. For example, although no statistical advantage was found for sodium hyaluronate in the intent to treat analysis of subjects whose contralateral knee pain score was greater than 12, 69% of all patients treated with sodium hyaluronate who completed 27 weeks of the study achieved clinically meaningful improvement, as defined by a 15% improvement in summed Western Ontario and McMaster Universities Osteoarthritis Index pain score averaged across Weeks 7 to 27, in comparison with their baseline score.

In the current study and the Hyalgan clinical trial reported by Altman and Moskowitz,[4] a large placebo effect was observed for pain during a 50-foot walk and various Western Ontario and McMaster Universities Osteoarthritis Index scales. In the intent to treat analysis, no significant advantage of Hyalgan relative to the control was observed in pain during a 50-foot walk.[4] In addition, no benefit of naproxen over placebo was apparent in the intent to treat population at any time in the study. Although the investigators reported a benefit of Hyalgan over placebo in the patients who completed the study, no predictors of a favorable response to Hyalgan were apparent. Thirty percent of patients in the Hyalgan group of that study, but only 20% in the sodium hyaluronate group of the current study, withdrew before completing the study.

No improvement in contralateral knee pain was observed after sodium hyaluronate treatment of the index knee. Given that sodium hyaluronate is administered locally, this was expected. In contrast, nonsteroidal antiinflammatory drugs, which are delivered systemically, may have a beneficial effect on pain in the index and contralateral knee, although the long-term benefit of nonsteroidal antiinflammatory drugs has been questioned.[13]

The incidence, type, and severity of adverse events in the two treatment groups in the current study were similar, suggesting that the adverse events were attributed to the injection and not to the material injected. The safety profile of intraarticular ORTHOVISC injection compares favorably with that of other intraarticular hyaluronic acid formulations. The incidence of adverse events in these other studies has been as high as 27% and often involved a local inflammatory reaction, occasionally with purulent (pseudoseptic) joint effusion.[29,37] In addition, no patients in the current study dropped out as a result of pain at the injection site. The higher incidence of adverse events in these other studies[29,37] may reflect differences in hyaluronate product formulation, product purity, or injection technique.

In patients with moderate pain in the knee with osteoarthritis whose baseline Western Ontario and McMaster Universities Osteoarthritis Index pain score for the contralateral knee was less than 12, intraarticular sodium hyaluronate was significantly more effective than the saline control, as reflected by improvement in Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and function scores, and 50-foot walk time. Many of the benefits of sodium hyaluronate persisted far beyond the duration that exogenous sodium hyaluronate has been shown to remain within the knee after injection. Additional studies are needed to explain

the mechanism of action underlying the clinical efficacy of this treatment. Sodium hyaluronate was well tolerated, and no complications were seen in conjunction with the treatment. Because the sodium hyaluronate used in the current study is a highly purified form of a natural compound, it may provide a safety advantage over similar products that contain chemical additives or crosslinking agents that could elicit an immunologic or inflammatory response. The data presented suggest intraarticular sodium hyaluronate may represent a well tolerated alternative to nonsteroidal antiinflammatory drugs and intraarticular injection of corticosteroids, and may provide sustained benefit for patients with moderate pain from osteoarthritis of the knee.

Acknowledgments

The authors thank the following investigators who, in addition to the authors, composed the ORTHOVISC Study Group, and without whom this trial could not have been completed: Sicy Lee, MD, and Steven Abramson, MD (Hospital for Joint Disease, New York, NY); Roy D. Altman, MD (University of Miami School of Medicine, Miami, FL); Howard Offenberg, MD (Halifax Hospital, Daytona Beach, FL); Michael Burnette, MD (Tampa, FL); Roland Moskowitz, MD, and Chad Deal, MD (University Hospitals of Cleveland, Cleveland, OH); David H. Neustadt, MD, PSC, and Stephanie Walton, MD (Louisville, KY). The authors also acknowledge the BBI project team, comprised of Kenneth Sciarappa, Patti Durkan, and Jeffrey Martin for data management and statistical analyses.

References

1. Adams ME: An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. J Rheumatol 39(Suppl):16–18, 1993.
2. Adams ME, Atkinson MH, Lussier AJ, et al: The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage 3:213–225, 1995.
3. Altman R, Asch E, Bloch D, et al: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 29:1039–1049, 1986.
4. Altman RD, Moskowitz R: Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial. J Rheumatol 25:2203–2212, 1998.
5. Balazs E, Denlinger JL: Viscosupplementation: A new concept in the treatment of osteoarthritis. J Rheumatol 20(Suppl 39):3–8, 1993.
6. Beadling L: Hyaluronic acid products: What they are, how they work. Orthop Today 17:1–2, 1997.
7. Belcher C, Yaqub R, Fawthrop F, et al: Synovial fluid chondroitin and keratan sulphate epitopes, glycosaminoglycans, and hyaluronan in arthritic and normal knees. Ann Rheum Dis 56:299–307, 1997.
8. Bellamy N: WOMAC Osteoarthritis Index: A Users Guide. London, Ontario, Victoria Hospital 1995.
9. Bellamy N: Validation study of a computerized version of the Western Ontario and McMaster Universities VA3.0 Osteoarthritis Index. J Rheumatol 12:2413–2415, 1997.
10. Brandt KD, Smith GN, Simon LS: Intra-articular injection of hyaluronic acid as treatment for knee osteoarthritis. What is the evidence? Arthritis Rheum 43:1192–1203, 2000.
11. Creamer P, Hunt M, Dieppe P: Pain mechanisms in osteoarthritis of the knee: Effect of intraarticular anesthetic. J Rheumatol 23:1031–1036, 1996.
12. Cunningham LS, Kelsey JL: Epidemiology of musculoskeletal impairments and associated disability. Am J Public Health 74:574–579, 1984.
13. Dieppe P, Cushnaghan J, Jasani MK, et al: A two-year, placebo-controlled trial of non-steroidal anti-inflammatory therapy in osteoarthritis of the knee joint. Br J Rheumatol 32:595–600, 1993.
14. Dixon AS, Jacoby RK, Berry H, et al: Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Curr Med Res Opin 11:205–213, 1988.
15. Duogados M, Nguyen M, Listrat V, et al: High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: A 1 year placebo-controlled trial. Osteoarthritis Cartilage 1:97–103, 1993.
16. Frizziero L, Govoni E, Bacchini P: Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: Clinical and morphological study. Clin Exp Rheumatol 16:441–449, 1998.
17. International Conference on Harmonisation: ICH Harmonised Tripartite Guideline: E6: Good Clinical Practice: Consolidated Guideline (62 Federal Regulations 25691). The United States Food and Drug Administration. http://www.fda.gov/cdrh/devadvice/part820.html, 2000.
18. Jones AC, Pattrick M, Doherty S, et al: Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage 3:269–273, 1995.
19. Kalay S: The Effectiveness of Intraarticular Hyaluronic Acid Treatment in Primary Gonarthrosis. MD Thesis. Ankara, Turkey, Ankara Numune Hospital, Physical Therapy and Rehabilitation Clinic 1997.
20. Lawrence JS, Bremner JM, Bier F: Osteo-arthritis prevalence in the population and relationship between symptoms and x-ray changes. Ann Rheum Dis 25:1–24, 1996.

21. Leardini G, Mattara L, Franceschini M, et al: Intra-articular treatment of knee osteoarthritis: A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. Clin Exp Rheumatol 9:375–381, 1991.
22. Lindenhayn K, Heilmann HH, Niederhausen T, et al: Elimination of tritium-labelled hyaluronic acid from normal and osteoarthritic rabbit knee joints. Eur J Clin Chem Clin Biochem 35:355–363, 1997.
23. Ling SM, Bathon JM: Osteoarthritis in older adults. J Am Geriatr Soc 46:216–225, 1998.
24. Listrat V, Ayral X, Patarnello F, et al: Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cartilage 5:153–160, 1997.
25. Lohmander LS, Dalen N, Englund G, et al: Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Ann Rheum Dis 55:424–431, 1996.
26. Lussier A, Cividino AA, McFarlane CA, et al: Viscosupplementation with hylan for the treatment of osteoarthritis: Findings from clinical practice in Canada. J Rheumatol 23:1579–1585, 1996.
27. Peyron JG: Intraarticular hyaluronan injections in the treatment of osteoarthritis: State-of-the-art review. J Rheumatol 39(Suppl):10–15, 1993.
28. Praemer A, Furner S, Rice DP: Costs of Musculoskeletal Conditions. Musculoskeletal Conditions in the United States. Park Ridge, IL, Grune & Stratton 145–170, 1992.
29. Puttick MP, Wade JP, Chalmers A, et al: Acute local reactions after intraarticular hylan for osteoarthritis of the knee. J Rheumatol 22:1311–1314, 1995.
30. Scholes D, Stergachis A, Penna PM, et al: Nonsteroidal antiinflammatory drug discontinuation in patients with osteoarthritis. J Rheumatol 22:708–712, 1995.
31. Sieliwonczyk P, Mazurkiewicz O, Ostojski R, et al: Evaluation of the value of intraarticular Hyalgan infections for treatment of knee joint osteoarthritis. Chir Narzadow Ruchu Ortop Pol 62:337–342, 1997.
32. Smith MM, Ghosh P: The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. Rheumatol Int 7:113–122, 1987.
33. Tekeoglu I, Adak B, Goksoy T, et al: Effects of intra-articular injections of sodium hyaluronate (Orthovisc) and betamethasone on osteoarthritis of the knee. J Rheumatol Med Rehabil 9:220–224, 1998.
34. US Food and Drug Administration/(FDA)/Center for Devices and Radiological Health (CDRH) resources page. United States Food and Drug Administration Web site. http://www.fda.gov/cdrh/devadvice/part820.html. 2000.
35. Wobig M, Dickhut A, Maier R, et al: Viscosupplementation with hylan G-F 20: A 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 20:410–423, 1998.
36. Wu JJ, Shih LY, Hsu HC, et al: The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Chung Hua I Hsueh Tsa Chih (Taipei) 59:99–106, 1997.
37. Yaoyshyn EA, Matteson EL: Gout after intraarticular injection of hylan GF-20 (Synvisc). J Rheumatol 26:2717, 1999. Letter.