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ORIGINAL ARTICLE

Efficacy and Safety of Hyaluronan Treatment in Combination Therapy With Home Exercise for Knee Osteoarthritis Pain

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ABSTRACT. Stitik TP, Blacksin MF, Stiskal DM, Kim JH, Foye PM, Schoenherr L, Choi E-S, Chen B, Saunders HJ, Nadler SF. Efficacy and safety of hyaluronan treatment in combination therapy with home exercise for knee osteoarthritis pain. Arch Phys Med Rehabil 2007;88:135-41.

Objective: To assess the efficacy and safety of intra-articular injections of sodium hyaluronate combined with a home exercise program (HEP) in the management of pain associated with osteoarthritis (OA) of the knee.

Design: Single-blinded, parallel-design, 1-year clinical study with sequential enrollment.

Setting: University-based outpatient physiatric practice.

Participants: Sixty patients (18 men, 42 women; age, ≥50y) with moderate-to-severe pain associated with OA of the knee.

Interventions: (1) Five weekly intra-articular hyaluronate injections (5-HYL); (2) 3 weekly intra-articular hyaluronate injections (3-HYL); or (3) a combination of an HEP with 3 weekly intra-articular hyaluronate injections (3-HYL+HEP).

Main Outcome Measures: The primary outcome measure was a 100-mm visual analog scale for pain after a 50-foot walk (15.24m). Secondary measures included the Western Ontario and McMaster Universities Osteoarthritis Index subscales.

Results: The 3-HYL+HEP group had significantly faster onset of pain relief compared with the 3-HYL ($P<.01$) and 5-HYL groups ($P=.01$). All groups showed a mean symptomatic improvement from baseline (reduction in baseline pain at 3mo was 59%, 49%, and 48% for the 3-HYL+HEP, 3-HYL, and 5-HYL groups, respectively) that was clinically and statistically significant. There were no between-group differences in the incidence or nature of adverse events.

Conclusions: The combined use of hyaluronate injections with HEP should be considered for management of moderate-to-severe pain in patients with knee OA.

Key Words: Exercise; Hyaluronic acid; Injections, intra-articular; Osteoarthritis; Rehabilitation.

KNEE OSTEOARTHRITIS (OA) IS AMONG the most common causes of musculoskeletal pain and disability in the United States.[1-4] At present there is no cure for OA. Therefore, the primary aims of therapy are to reduce pain, maintain or improve function and mobility, and prevent or slow the progression of adverse changes to the joint tissues, while keeping potential therapeutic toxicities to a minimum.[1-4] Current treatment guidelines begin with nonpharmacologic modalities, such as patient education, weight loss, and physical therapy.[1,4]

Several exercise-based therapeutic approaches, such as aerobic exercise programs, range-of-motion exercises, and muscle-strengthening exercises are recommended and have been shown to have clinical benefit in randomized, controlled clinical trials.[1,4] For example, Thomas et al[5] have reported significant improvement in the pain and function subscores of the Western Ontario and McMaster Universities (WOMAC) outcome measure with a home exercise program (HEP), and isometric quadriceps exercises for 3 months have been shown to decrease pain due to knee OA.[6]

Nonpharmacologic approaches frequently provide insufficient pain relief and restoration of function and mobility, and pharmacologic modalities become necessary. Although simple analgesics such as acetaminophen provide relief for many OA patients with mild to moderate pain, alternatives should be considered for patients who fail to obtain adequate symptomatic relief with these measures.[1,3,4] Although nonsteroidal anti-inflammatory drugs and/or cyclo-oxygenase 2 (COX-2) selective inhibitors are frequently efficacious for the relief of moderate to severe OA pain, these options are not always effective, and may be inappropriate in patients with gastrointestinal or cardiovascular risk factors.[1,7-10]

Sodium hyaluronate (Hyalgan; molecular weight, 500–730kDa; 20mg in 2mL), given as 3 or 5 weekly intra-articular injections, has been shown to be efficacious and well tolerated for the treatment of pain associated with OA of the knee.[11-14] Moreover, recent evidence suggests that in addition to its pain-relieving characteristics, intra-articular sodium hyaluronate may also exert biochemical effects that help retard the progression of joint changes.[15] This local therapeutic option is currently recommended by a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials for patients who have not responded optimally to nonpharmacologic measures and simple analgesic therapy (ie, acetaminophen).[1,4]

It is generally accepted that optimal management of knee OA requires a combination of pharmacologic and nonpharmacologic treatment modalities.[1,4] Although few studies have directly evaluated the benefits of combining the 2 modalities in randomized, controlled fashion, there is indirect evidence that nonpharmacologic therapies can offer additional benefit over and above analgesics alone.[4] For example, in 1 study, patients who had been taking simple analgesics at baseline showed a significant benefit of adding an HEP that focused on quadriceps strengthening.[16]

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The established clinical benefits of quadriceps-strengthening exercises and intra-articular injections of hyaluronans when used separately have already been shown.[11-14,17-21] One of these studies even compared intra-articular injections of hyaluronans with progressive resistive knee exercises.[14] The current study, therefore, was not designed to reexamine the benefits of exercise alone or compare these benefits with those from intra-articular injections of hyaluronans. In contrast, because the concomitant use and potential additive or synergistic effects of exercise and intra-articular injections of hyaluronans have not been adequately studied, this study investigated the potential benefit of combining an HEP with weekly intra-articular hyaluronate therapy.

METHODS

Study Design

This was a single-center, single-blind, parallel-design, 1-year study. We screened consecutive patients presenting with pain associated and clinically diagnosed knee OA for study participation after they provided written informed consent. Recruitment continued until 60 patients were enrolled (18 men, 42 women). Eligible patients were sequentially assigned to 1 of 3 treatment groups. The first patient was assigned to group 1 (3 weekly intra-articular hyaluronate injections [3-HYL]), the second to group 2 (3 weekly intra-articular hyaluronate injections combined with an HEP [3-HYL+HEP]), and the third to group 3 (5 weekly intra-articular hyaluronate injections [5-HYL]). The enrollment of subsequent patients followed the same pattern (ie, the fourth patient was assigned to group 1, the fifth to group 2, and so forth). The primary physician injectors were blinded to the treatment assignments and did not participate in any of the clinical assessments by the blinded observer.

There was a 7- to 14-day washout period between screening and baseline assessments during which analgesics were withdrawn to ensure that candidates would tolerate using only acetaminophen as needed for pain. All patients were supplied with 500-mg acetaminophen tablets for rescue analgesia (4g/d maximum allowed use) of pain in the treated knee only. All other analgesics were prohibited. Patient diaries were reviewed at each follow-up visit to ensure that they were taking no more than 4g/d. Noncompliant patients were to be removed from the study.

This 1-year study required the participation of both blinded and nonblinded physicians. Blinded physicians performed the first 3 weekly intra-articular hyaluronate injections on all patients and all subsequent follow-up examinations. The nonblinded physicians performed the remaining 2 knee injections on the patients in the 5-HYL group and reviewed HEP performance in the 3-HYL+HEP group. At all injection visits, patients were asked if they had any injection-related pain or complications, and their responses were recorded.

Participants

Inclusion criteria were as follows: men or women 50 years or older with a diagnosis of knee OA according to the American College of Rheumatology criteria for the classification of knee OA and Kellgren-Lawrence grade 2 or 3 by radiograph.[22,23] Eligible patients currently taking regular doses of analgesic medications had to report a knee pain severity score of 30 to 90mm (100-mm visual analog scale [VAS]) after a 50-foot walk (15.24m) at screening. Patients not taking regular doses of analgesics had to report a pain score of 40 to 90mm. Patients agreed to use only acetaminophen (up to 4g/d) for rescue pain and to continue any pre-existing nonpharmacologic pain management regimen, such as use of an assistive device, during the study. In addition, eligible patients could not have received intra-articular hyaluronate therapy within the previous 6 months. In cases of bilateral OA, the more severely affected knee, as judged by the VAS score at screening, was designated the knee for treatment.

We excluded patients if they had one of the following: a known cause of secondary OA; previous significant knee surgery to the study knee; active acquired immune deficiency syndrome (or were positive for human immunodeficiency virus); severe hypertension; current anticoagulant therapy; a history of inflammatory arthropathy; gout, or pseudogout of the knee with a flare within 12 months; or were women of childbearing potential and not willing to use contraceptive prophylaxis.

Interventions

Patients received a total of either 3 (3-HYL, 3-HYL+HEP) or 5 (5-HYL) weekly (every 5−9d) intra-articular injections of hyaluronate in the study knee. We administered injections at the baseline visit.

The HEP consisted of 2 different exercises designed to strengthen the anterior thigh muscles (quadriceps setting exercises, wall slides), performed on alternating days. We instructed the patient to perform 3 to 5 sets of 8 to 12 repetitions per set per knee of quadriceps setting exercises, as well as 3 to 5 sets of 8 to 12 repetitions per set of wall slides. After patients watched an instructional videotape, the study coordinator demonstrated the exercises and watched the patients perform them, making necessary adjustments to their techniques. This is considered a simple HEP because it did not require patients to attend a formal physical therapy (PT) program to learn the exercises, nor was any special equipment needed. Any difficulties with the exercises were monitored through questioning and addressed at each visit. Patients were instructed not to exercise on the days when they would receive hyaluronate injections.

Outcomes

The primary efficacy measurement was VAS pain score, recorded immediately after a 50-foot walk at the screening and baseline visits, the 3- or 5-injection weekly visits, and at months 3, 6, 9, and 12. The WOMAC Osteoarthritis Index total and subscales (pain, function, stiffness) were secondary efficacy parameters recorded at baseline, week 1, week 3, and at months 1, 3, 6, 9, and 12. Efficacy parameters and safety data were assessed immediately before each injection.

Each injection visit took place 7 days (±2d) after the previous injection, and all injections were to be completed within 5 weeks. Follow-up visits occurred 1 month (+1wk) after the third injection. Patients who did not attend visits within the specified time frames were removed from the study, and their data for the primary endpoint (ie, VAS pain after the 50-foot walk) as well as the WOMAC total and subscales were analyzed with the last observation carried forward (ie, intent-to-treat [ITT] analysis).

Statistical Analysis

We used a longitudinal, repeated-measures design based on a mixed-effects model to evaluate change from baseline and to make between-group comparisons for the continuous outcome variables (VAS pain; WOMAC pain, function, and total scores) at each time point. Factors included treatment group, visit week, treatment-by-week interaction, and baseline VAS assessment (as covariate). Baseline comparability between treatment

Table 1: Baseline Demographics and Disease Characteristics

Parameter	Group			
	3-HYL	3-HYL+HEP	5-HYL	Total
Age (y)	62.5±9.3	64.7±8.1	65.5±10.4	64.2±9.2
No. of patients/age group (y)				
50–62	11	7	9	27
63–70	4	7	5	16
70+	5	6	6	17
No. patients by VAS pain				
Moderate (30–60mm)	13	12	13	38
Severe (>60–90mm)	7	8	7	22
No. men/women	5/15	7/13	6/14	18/42
Weight (kg)	98.8±24.3	91.5±18.8	106.3±21.7	98.8±22.3
No. patients reporting regular use of oral analgesics	16/20	12/20	14/20	42/60
VAS pain	47.3±16	49.3±24.3	50.6±27.7	49.1±22.9
WOMAC pain	12.1±4.4	10.8±5.2	10.8±4.9	11.2±4.8
WOMAC function	40.3±14.0	31.0±15.4	35.8±17.1	35.6±15.8
WOMAC total	57.0±18.6	46.3±21.7	51.7±22.6	51.6±21.2

NOTE. Values are mean ± standard deviation (SD) or as otherwise indicated.

groups was tested by analysis of variance. All tests were conducted at an α level of .05 and 80% power.

We evaluated the primary endpoint (VAS score after a 50-foot walk) as well as the WOMAC subscales and total using an ITT population, defined as all patients who had baseline data, and who received at least 1 dose of study medication and 1 postbaseline measurement. Last observation carried forward was used for patients who did not complete the study. For the primary endpoint, parallel analyses of observed population and completers were conducted. Observed population was defined as all patients who participated in the study and had data points at baseline and at least 1 postbaseline value. For this analysis, no data points were carried forward if a patient missed any assessment. Completer patients were defined as those who had completed the study and had data collected at all primary efficacy data points (baseline, weeks 1 and 3, and months 1, 3, 6, 9, and 12).

Institutional Review Board

The protocol, any amendments, advertisements, and the patient's informed consent form were reviewed and approved by the university institutional review board (IRB). All adverse events and any significant deviations from the protocol were promptly reported to the IRB.

RESULTS

Study Population Demographics and Baseline Disease Characteristics

Table 1 summarizes patient demographic characteristics for each of the 3 groups. Between the groups, no statistically significant differences were found for age, sex, body weight, and baseline analgesic consumption. Furthermore, patients in the treatment groups did not show any statistically significant differences in VAS pain scores after a 50-foot walk, or in WOMAC pain, WOMAC function, or WOMAC total. Overall, all patients had a mean baseline VAS score of 49.1mm, which was categorized as moderate-to-severe pain.[24]

Patient Disposition

Among the 60 enrolled patients, 8 (13.3%) discontinued prematurely due to protocol deviations prior to the month 6 visit, and a total of 32 (53.3%) discontinued prematurely due to protocol deviations prior to the 1-year final visit: 11 in the 3-HYL group, 11 in the 3-HYL+HEP group, and 10 in the 5-HYL group (table 2). No patient withdrew consent during the study. Proportions of discontinuations did not differ significantly among the groups ($P=.93$). A subanalysis of the analgesic noncompliant patients revealed that 4 patients in the 3-HYL group and 1 patient in the 5-HYL group violated the protocol and were excluded from efficacy analyses; no patient in the 3-HYL+HEP deviated from the protocol with regard to analgesic use.

Primary Efficacy Outcome Measure: VAS Pain on the 50-Foot Walk Test

Onset of pain relief. Both the 3-HYL+HEP and the 5-HYL groups exhibited statistically significant improvement (58.0%, 30.2%, respectively) from baseline in VAS pain on the 50-foot walk test by week 2 ($P<.001$, $P=.004$, respectively). In contrast, the 3-HYL group eventually showed a statistically significant improvement (29.0%, $P=.006$) by week 7. In a secondary analysis of the primary outcome of the VAS pain score, clinically significant pain relief (>50% reduction in mean VAS from baseline) was reached by week 2, for the 3-HYL+HEP group (58.0%) compared with 14.2% and 30.2% for the 3-HYL and the 5-HYL groups, respectively. This represented a significant difference for the 3-HYL+HEP group compared with the 3-HYL and 5-HYL groups ($P\leq.01$ for both comparisons). A 50% improvement in VAS pain after the 50-foot walk test was eventually observed by week 11 for patients in the 3-HYL and 5-HYL groups.

Duration of pain relief. For patients in the 3-HYL+HEP group, reductions from baseline in mean VAS pain score were statistically significant from week 2 ($P<.01$) through the last follow-up visit at week 52 ($P<.05$). For patients in the 3-HYL group, reduction from baseline in mean VAS pain score was not significant at week 39 ($P=.15$), at which time this group did significantly poorer ($P<.05$) than the 3-HYL+HEP and the 5-HYL groups. The reduction from baseline in mean VAS pain score, however, was significant at week 52 ($P<.05$) for the 3-HYL group. For patients in the 5-HYL group, reductions from baseline in mean VAS pain score at week 52 were significantly better than the 3-HYL group ($P<.05$), but there

Table 2: Reasons for Study Discontinuation

Category	Study Withdrawals (mo)					
	3-HYL		3-HYL+HEP		5-HYL	
	1–6	7–12	1–6	7–12	1–6	7–12
Major protocol deviation	0	4	0	0	1	0
Analgesic medication	0	0	0	0	1	0
Underwent TKR	NA	NA	1	0	NA	NA
Inability to tolerate the exercise regimen	0	0	0	1	0	0
Meniscal surgery on study knee after injury unrelated to study	0	1	1	0	0	0
Unable to tolerate isokinetic testing	1	1	0	1	0	2
Unrelated concurrent medical illness*	2	2	1	6	0	6
Investigator-initiated withdrawal†	0	0	0	0	0	0
Patient withdrawal of consent	3	8	3	8	2	8
Subtotals	11		11		10	
Totals						

Abbreviations: NA, not applicable; TKR, total knee replacement.
*Influenza virus (4 patients); myocardial infarction (1 patient).
†Patient did not attend visit within specified time period.

were no statistically significant differences between the 3-HYL+HEP and 5-HYL groups (fig 1).

Clinically significant pain relief (ie, greater than 20% improvement in VAS) was maintained in the majority of patients in each treatment group during the 52-week study.[24] The percentage improvement in mean VAS pain score for each of the 3 groups was maintained through month 6 and month 12, with a somewhat higher percentage seen in the 3-HYL+HEP treatment group: by month 6, 58.2%, 48.6%, and 39.1% of patients in the 3-HYL+HEP, 3-HYL, and 5-HYL groups, respectively, experienced reduction in pain as shown by mean VAS pain score. At month 12, the percentages of patients experiencing clinically significant pain reduction were 46.2%, 35.7%, and 55.6%, respectively.

Secondary Endpoints

WOMAC index: subscales and total. All treatment groups exhibited significant mean improvements at week 52 from baseline in the WOMAC function, WOMAC pain, and WOMAC total scores. Significant mean improvements were not found for WOMAC stiffness scores. Pairwise comparison did not indicate any significant between-treatment group differences for WOMAC pain (fig 2A), or WOMAC function (fig 2B) except at week 52, at which time the 3-HYL+HEP group did significantly better than the 3-HYL group (WOMAC pain, $P<.01$; WOMAC function, $P<.05$). At week 52, there was no significant difference between the 3-HYL+HEP and the 5-HYL groups. Although there were no significant differences among treatment groups in the WOMAC total score at any time period (table 3), there was a numerically greater improvement for the 3-HYL+HEP group at week 52. This numerically greater improvement in the WOMAC total score in the 3-HYL+HEP group was due to improvement in both the WOMAC pain and function subscores (see figs 2A, 2B; table 3).

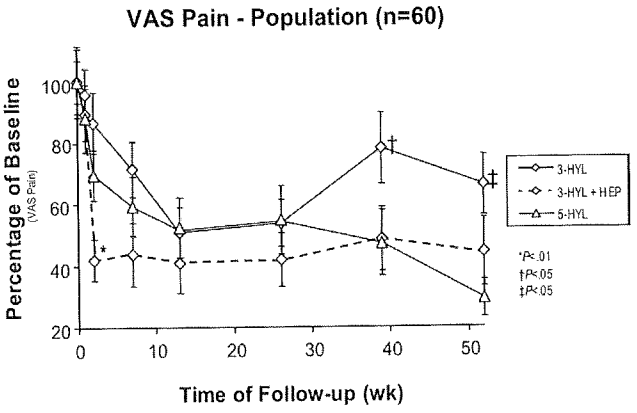

Fig 1. VAS pain improvement from baseline through 12 months. Each point represents the mean VAS pain score ± standard error of the mean (SEM) normalized to the baseline VAS pain score for each treatment group—3-HYL, 3-HYL+HEP, and 5-HYL—at each of 6 follow-up visits through 12 months. Statistical differences noted at the respective time points: *$P<.01$, comparing 3-HYL+HEP with 3-HYL or 5-HYL; †$P<.05$, comparing 3-HYL+HEP and 5-HYL with 3-HYL; ‡$P<.05$, comparing 3-HYL with 5-HYL.

Exercise Compliance

We were unable to analyze data from the exercise diaries. About 50% of the subjects did not return or complete their final diaries as directed.

Safety Data

Reasons for study discontinuation are shown in table 2. There were no product-related severe adverse events reported. No patient withdrew due to injection site pain. There were no statistically significant differences observed between the treatment groups with respect to the overall incidence of adverse events. One patient was unable to tolerate the HEP due to a pre-existing abdominal wall hernia and withdrew from the study. The following major medical problems arose during the study, but were not considered by the investigator to be related to any study intervention: 1 patient had a myocardial infarction; 1 patient twisted his knee and required a subsequent arthroscopic partial meniscectomy; and 4 patients contracted influenza. Each of these patients withdrew from the study. Subjects were required to attend a follow-up visit within a certain narrow window of time as explained in the Methods section of this study. Subjects who did not attend a follow-up visit within that narrow window were removed from further study participation. This category of study withdrawal was labeled as "investigator-initiated withdrawal," accounting for 16 of the 32 subjects who dropped out.

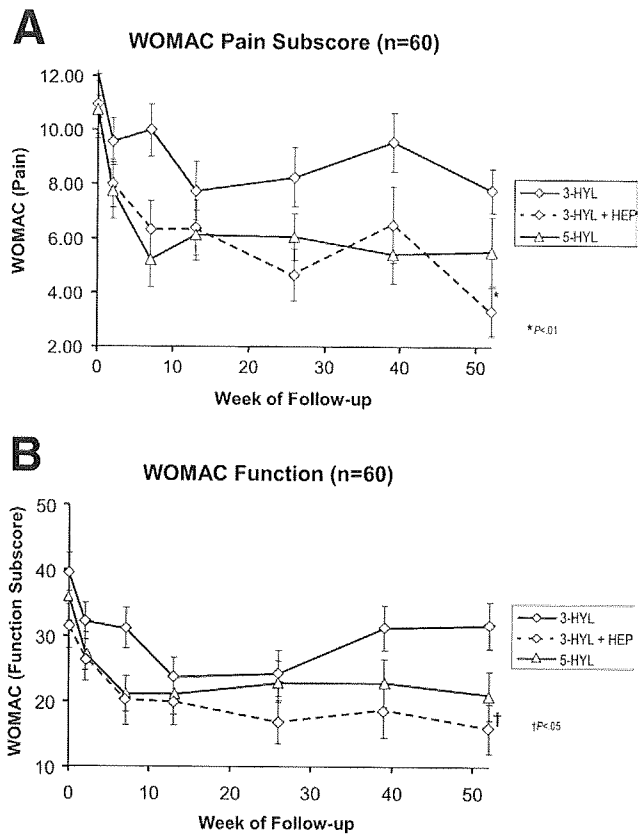

Fig 2. WOMAC pain and function domains from baseline through 12 months. Each point represents the (A) mean WOMAC pain domain score ± SEM or (B) mean WOMAC function domain score ± SEM function for each treatment group—3-HYL, 3-HYL+HEP, and 5-HYL—at each of 6 follow-up visits through 12 months. Statistical differences noted at the respective time points: *$P<.01$, comparing 3-HYL+HEP with 3-HYL; no significant differences were found between 3-HYL+HEP with 5-HYL or between 5-HYL with 3-HYL at 52 weeks; †$P<.05$, statistically significant improvement at week 52 for the 3-HYL+HEP group versus the 3-HYL group; no significant differences were found between the 3-HYL+HEP and 5-HYL groups, or between the 5-HYL and 3-HYL groups at 52 weeks.

DISCUSSION

All 3 interventions in this study—3-HYL, 3-HYL+HEP, and 5-HYL—produced statistically significant reductions from baseline in mean VAS pain score; furthermore, clinically significant functional improvements were observed for all treatment groups. The incorporation of a simple HEP with hyaluronate therapy resulted in significantly improved clinical outcomes compared with hyaluronate therapy alone with regard to onset and duration of pain relief. There was a statistically significantly faster onset, greater peak effect, and longer duration of pain relief in patients on HEP compared with patients who received a comparable number of intra-articular hyaluronate injections, but did not participate in HEP.

This study is among the first to show that there may be an additive benefit when using a nonpharmacologic intervention (ie, HEP) as adjunct therapy to intra-articular hyaluronate in the management of pain associated with OA of the knee; however, exercise itself may have provided a lot of benefit seen in the intra-articular hyaluronate plus exercise group, because there was no treatment allocation to exercise alone in this study. In addition, because patients in the exercise group could not be blinded, they could have been influenced positively by getting more treatment in the combined treatment arm. A recent publication[25] reported a significant benefit of isokinetic exercise, pulse ultrasound, and intra-articular sodium hyaluronate therapy for the treatment of pain and functional disability, but did not evaluate intra-articular hyaluronan plus exercise alone (in the absence of pulse ultrasound therapy). The tentative conclusion of additive or synergistic benefit is supported on 2 levels. First, the 3-HYL+HEP group had a significantly more rapid onset of pain relief compared with the 3-HYL group ($P<.01$) and the 5-HYL group ($P=.01$). Second, the 3-HYL+HEP group had greater pain relief starting at month 1, which was sustained through month 12 compared with the 3-HYL group, which only had pain relief through month 6, and similar pain relief when compared with the 5-injection regimen. This finding suggests that an additive benefit of intra-articular hyaluronate with an HEP may allow for the administration of fewer injections. Despite these promising findings, however, differences in duration of effect should be interpreted with caution, because the drop-out rate at the 12-month time point was high (32/60 patients overall). The fact that the trial was not truly randomized could have theoretically led to potential selection bias, although the baseline characteristics of the groups were not statistically significantly different.

All 3 treatment groups in this study exhibited a combined VAS pain score improvement in the ranges of 41% to 59%, 39% to 58%, and 46% to 56% at 3, 6, and 12 months of follow-up, respectively. These ranges exceed the symptomatic improvement that would be considered clinically significant.[26-29] Similar improvement ranges in the patients' WOMAC pain subscores were also observed at 3, 6, and 12 months.

In addition to pain relief, all 3 subgroups reported functional improvement based on the WOMAC functional subscore throughout the study. This finding is consistent with the results of previous studies that have reported improved function scores with both intra-articular hyaluronate therapy[30-32] and an HEP.[33,34] This study further showed that 3-HYL and 5-HYL provide equivalent clinical benefits through 6 months of treat-

Table 3: Change in Mean Total WOMAC Score Within Treatment Groups at Baseline Versus Follow-Up Visits for ITT Population

	Improvement from Baseline in Total WOMAC Score by Visit					
Treatment Group	Baseline	1 Month (wk 7)	3 Months (wk 12)	6 Months (wk 26)	9 Months (wk 39)	12 v (wk 52)
3-HYL	NA	11.58±4.3	20.53±4.4	19.90±4.6	12.16±5.2	12.32±5.1
		P=.010	**P<.001**	**P<.001**	**P=.024**	**P=.020**
3-HYL+HEP	NA	20.31±4.2	19.81±4.3	23.76±4.5	21.61±5.1	26.11±5.0
		P<.001	**P<.001**	**P<.001**	**P<.001**	**P<.001**
5-HYL	NA	22.38±4.2	20.73±4.2	19.28±4.4	19.08±5.0	21.18±4.9
		P<.001	**P<.001**	**P<.001**	**P<.001**	**P<.001**

NOTE. Values are mean ± SD. A positive value indicates improvement compared with baseline. Significant *P* values are shown in bold.

ment, consistent with previous findings that the 2 regimens provide similar efficacy over a short time course.[13]

Recently, Ravaud et al[35] reported on the use of an unsupervised HEP in the management of OA knee pain and found no clinically relevant short-term benefit of the exercise program. This contrasts with the previous findings of significant improvements in the pain and function subscores of the WOMAC outcome measure.[5,36] Unlike those studies, however, the current study was designed to identify additive benefits of HEP rather than the benefits of HEP alone. Huang et al[25] found that isokinetic strengthening exercise and intra-articular hyaluronan therapy were beneficial in the treatment of knee OA in conjunction with pulse ultrasound therapy. With respect to use of exercise as a primary treatment modality, Baker et al[37] showed that a high-intensity, home-based strength-training program produced substantial improvements in pain, physical function, and quality of life. In Ettinger's Fitness and Arthritis Seniors Trial,[38] patients who underwent quadriceps-strengthening exercises showed a modest improvement in pain. In terms of adjunctive therapy, Bayramoglu et al[20] combined quadriceps strengthening as part of a formal PT program with 2 different intra-articular hyaluronans and found reductions in pain of 4.8 and 4.2, respectively, as measured by the index of severity for knee OA. In this same study, the PT-only group also experienced pain reduction but with an index of only 2.3.

Despite the clear clinical benefit noted, the precise mechanism by which a simple exercise program alone or as an adjunct therapy contributes to the observed beneficial effect is unknown. Miyaguchi et al[6] recently reported that isometric quadriceps exercises resulted not only in significant reduction in pain scores at week 12, but also a change in the biochemical profile of the synovial fluid. In that study, an increase of 14% in the average molecular weight of the hyaluronan and a 31% increase in viscosity of the patients' synovial fluid were observed. In addition, similar molecular changes have been noted in patients injected with hyaluronate.[39] This could provide a molecular explanation for the additive or synergistic effect seen between the 3-injection regimen of intra-articular hyaluronate injections and an HEP.

Another possible explanation for the improved clinical benefit with adjunct HEP may be that compressive forces increase across the knee during a closed chain kinetic-strengthening exercise, such as the wall slide.[40] One hypothesis is that these forces act to increase imbibition of hyaluronan into the cartilage, thus enhancing the biologic effects of hyaluronan. In addition, due to the nonvascular characteristics of articular cartilage, the compression and expansion of the cartilage matrix acts to draw in metabolites and wash out catabolites, thus maintaining chondrocyte viability. Galois et al[41] reported that although mild to moderate exercise in a rat OA model can reduce OA lesions, intense exercise negated the beneficial effects of exercise.

Study Limitations

There are several limitations to the generalization of the results of this study, including the drop-out rate, issues with exercise compliance, the long-term measurement of efficacy, and the lack of an exercise-only control group. Although the drop-out rate was acceptable through month 6 at 13.3% (8/60), the drop-out rate at month 12 was 53% (32/60) (see table 2); however, the majority of patients (17/32 [55%]) were removed from the study by the investigator because of significant protocol violations associated with failing to attend a scheduled follow-up visit within the specified time frame. Overall, only 6 patients (10%) could be considered treatment failures based on removal from the study by the investigators due to their need to take additional analgesics (n=5) or to undergo total knee replacement (n=1).

The failure to measure actual exercise compliance is a potentially severe limitation of this study. Compliance with HEP can be difficult to maintain in the long term; however, because a benefit was observed with HEP in this study, the issue of compliance would seem to argue that an underestimation, not overestimation, has been made for the benefits of HEP in this study.

Hyaluronate treatment was well tolerated in all groups, with no treatment-related severe adverse effects. None of the patients withdrew consent, and there were no intra-articular hyaluronate-related adverse events leading to discharge from the study. This is consistent with previous literature and clinical experience.[42,43] The issue of patient-related safety has recently become increasingly important with oral medications used in the management of OA pain, especially when considering recent findings associated with nonsteroidal anti-inflammatory drugs and COX-2 inhibitors for chronic pain management.[7,8]

Although additional confirmation of the apparently improved efficacy arising from a combined regimen of HEP and intra-articular hyaluronate therapy through a larger controlled study would be prudent, there seems to be very little risk in recommending an adjunct HEP to patients receiving intra-articular hyaluronate therapy. To assess this effect more accurately, compliance with exercise should also be measured in any future studies. It would be of interest to establish whether the excellent response and duration of the 5-HYL regimen could further be enhanced by an HEP, as it was with the 3-HYL regimen, because the 12-month duration of significant pain relief from a single 5-dose course of intra-articular hyaluronate injections was clinically significant.

CONCLUSIONS

The combined use of hyaluronate injections with HEP appeared to be more beneficial than hyaluronate injections alone in this population of patients with moderate-to-severe knee OA. A regimen such as this should be considered as part of the nonsurgical therapeutic armamentarium for chronic pain management of knee OA patients.

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