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Retrospective Study of Outcomes in Hyalgan®-Treated[1] Patients with Osteoarthritis of the Knee

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Abstract

Objective: To evaluate therapeutic success [defined as lack of total knee replacement surgery (TKR) or other significant clinical intervention during a 6-month follow-up] and to identify baseline patient and disease characteristics associated with improved pain relief and quality of life (QOL) in patients in a clinical practice who were treated with a single course of Hyalgan® (intra-articular hyaluronan) for pain associated with osteoarthritis (OA) of the knee.

Design and setting: This was an uncontrolled, retrospective study conducted at a single US clinical orthopaedic practice.

Patients: 248 patients with moderate to severe OA of the knee.

Intervention: All patients received a single course of intra-articular Hyalgan® therapy during an 18-month period, and had a radiogram of the treated knee within the 6 months before treatment.

Results: A total of 218 of 363 (60.1%) knees (248 patients) with moderate to severe OA were judged successfully treated over a 6-month follow-up period; only 20.3% of cases required TKR. On the basis of a multivariate analysis that correlated improvements in pain and QOL assessed by a retrospective questionnaire with baseline patient and disease characteristics, taller patients (>165cm), patients with less severe OA, and patients with patellofemoral compartment involvement had the greatest improvement in pain relief and quality of life following treatment with Hyalgan®.

Conclusions: Hyalgan® was effective in patients with moderate to severe OA, and may have delayed TKR in 80% of patients. Taller patients, patients with less severe OA, and patients with patellofemoral compartment involvement showed the greatest pain relief and improvements in QOL.

1 Use of tradenames is for product identification only and does not imply endorsement.

Hyaluronan (HA) is a major component of the synovial fluid and cartilage of the knee. It provides an extracellular matrix and hydrodynamic fluid with viscoelastic properties that allow for the efficient movement of articular joints.[1] Osteoarthritis (OA) of the knee is a chronic, progressive disease that can eventually lead to the destruction of the protective synovial lining and underlying articular cartilage layer. The biological matrix within the synovial fluid of the articular space is altered in OA, manifested as a decrease in total concentration and a decrease in the average molecular weight of the hyaluronans in the synovial fluid.[2] This observation led to the successful development of intra-articular HA injection as an approved therapy for the relief of pain in patients with OA of the knee who have not responded adequately to simple analgesics.[3]

Hyalgan® (sodium hyaluronate; FIDIA SpA, Padua, Italy), a 500 to 730kD molecular mass fraction of purified sodium hyaluronate, has been in clinical use in Europe since 1987, and has been approved in the USA since 1997 for the treatment of pain associated with OA of the knee. It is administered as a course of three or five intra-articular injections given at weekly intervals, and is currently the only intra-articular HA preparation with no safety restrictions in its label related to retreatment for recurring pain.[4,5] A number of randomised controlled clinical trials have demonstrated that the majority of patients treated with a single course of Hyalgan® receive clinical benefit for 6 to 12 months. [6-10] Hyalgan® was found to be significantly superior to placebo,[8,9,11] and at least as effective as naproxen, with fewer gastrointestinal adverse events.[8,9] However, in these studies, a fraction of patients were not responsive to therapy with Hyalgan® and, indeed, one randomised, controlled study in the literature failed to identify a benefit of Hyalgan® compared with placebo.[12] It is likely that a subset of nonresponsive patients will also be observed in clinical practice. In a retrospective study of outcomes in Canadian clinical practice with intra-articular Synvisc® (Hylan G-F 20), another HA product, approximately one-fourth of patients failed to show improvement after a single treatment course.[13] It would be useful to know the rate of therapeutic success of Hyalgan® in clinical practice, as well as to identify baseline factors that are predictive of a response to therapy, in order to help choose the most appropriate therapeutic modality from those available.

This study was a retrospective analysis of 300 clinical charts and x-rays of patients in a US clinical orthopaedic practice who received a single course of Hyalgan® with a 6-month follow-up for the relief of pain associated with OA of the knee. On the basis of independent review of the patients' charts and x-rays, the majority were considered candidates for total knee replacement (TKR) surgery prior to initiating Hyalgan® therapy. The objectives of this retrospective study were to evaluate the overall success of Hyalgan® therapy in a clinical setting, and to identify any associations between efficacy outcomes, such as improvement in quality of life (QOL) and pain relief, and demographic or baseline disease-related measurements.

Methods

Patients

All patients treated with Hyalgan® at the Florida Knee and Orthopedics Center (Clearwater, FL, USA) during an 18-month period were taken into consideration for the study. Eligible patients had a certain diagnosis of primary OA of the knee as established by American College of Rheumatology (ACR) criteria [14,15] and a radiogram of the treated knee within the 6 months before Hyalgan® treatment, which was obtained to establish the staging and compartmentalisation of OA. Grades and compartment classifications/patterns determined at the time of Hyalgan® therapy were confirmed retrospectively by an independent, blinded reviewer using the criteria of Barrett et al. [16]

Only patients who completed a single course of five intra-articular injections of Hyalgan® for pain associated with OA, and who were also available

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for at least a 6-month follow-up period, were included. Patients who received a second course of Hyalgan® within a 12-month period were not eligible, nor were those who had undergone a significant alteration in a routine exercise programme (routine = must have been in place for 6 months before initiation of Hyalgan®) within the 6-month follow-up after completion of Hyalgan® treatment. Eligible patients had charts available for a complete retrospective review, including access to x-rays of adequate quality, and had been free to receive intervention therapy at any time after Hyalgan® treatment.

Study Design

This was a retrospective study aimed at determining the effectiveness of Hyalgan® for preventing or delaying significant intervention therapy over a 6-month follow-up period, and at identifying any explanatory variables that might predict the efficacy of Hyalgan® treatment in patients with OA of the knee.

After eligibility for the study was determined, the patients were queried by a physician or healthcare professional over the phone as to their willingness to participate. Willing patients were asked, by a healthcare professional or clinician uninvolved in the initial clinical assessment or treatment, a total of 15 questions regarding their categorical rating of pain, stiffness and function, as well as general quality of life issue parameters before and after treatment (shown in Appendix 1). Significant clinical intervention therapy or TKR during the 6-month follow-up was noted. Other significant intervention therapies included intra-articular corticosteroid injection, arthrocentesis for removal of effusion, and clinically significant increase in dosage, frequency or duration of medication associated with the treated knee, as judged by the reviewer. Lack of TKR or other significant intervention therapy was considered the primary efficacy outcome for the study. Patients who had received intervention therapy were placed in the failure group.

Assessment of the following efficacy parameters was performed for each knee treated only among the cases who were judged to be successes: quality of life (QOL) [patient's global assessment], pain at night, and pain on walking, under load and at rest. Scores for these parameters were calculated on an ordinal scale from 1 (best) to 10 (worst). They were then reported as dichotomy variables (improvement *vs* non-improvement), constructed on the differences in the scores before and after treatment. When the value was 0 at baseline, the data were not considered in the analysis. Patients who reported a worsening or unchanged status compared with baseline were considered non-improvers. The relationships between these efficacy parameters and the following variables were then assessed using multivariate analysis: gender, baseline pain on walking (before treatment), the knee compartment involved, the radiographically determined degree of baseline OA severity, age, bodyweight and height. Consumption of drugs for treatment of OA was assessed descriptively before and after Hyalgan®.

Statistical Analysis

The following statistical analyses were performed: (i) descriptive analysis of the population by means and standard deviation or frequency; (ii) failure frequency (with special attention to the frequency of TKR); (iii) frequency and mean of improvements in QOL, night pain, and pain on walking, under load and at rest; (iv) logistic regression analysis using a stepwise procedure (considering a threshold level of 0.15) for analysis of the relationship between each efficacy measurement and potentially predictive variables. The variables that proved significantly associated with the efficacy parameters by logistic regression were analysed with a contingency table using Pearson's chi-square test at a significance level of 5%. Analyses were performed using SAS statistical software from SAS Institute, Cary, NC, USA.

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Results

Disease and Demographic Characteristics

The patient flow for the study is shown in figure 1. Of 539 knees (376 patients), 363 (249 patients) were available to be assessed. Of the 127 (33.8%) patients who failed to be interviewed, 26.3% (78% of non-participants) were lost to follow-up due to disconnected or wrong telephone numbers and only 7.5% (22% of non-participants) refused to co-operate. It appeared that loss to follow-up was a random event, so it was unlikely to have systematically affected outcomes. Of the 249 participants, 135 (54.2%) patients had unilateral OA of the knee and 114 (45.8%) patients had bilateral OA. Of 363 knees available for analysis, 218 (60.1%) knees were considered clinically improved, based on lack of TKR or clinically significant intervention. A total of 145 (39.9%) knees were considered therapeutic failures because they underwent TKR (20.3%) or were judged as a failure based on other intervention(s) recorded in the clinical notes (19.6%).

Table I. Baseline characteristics of patients

Characteristic	Study population (249 patients; 363 knees)
Mean (range) age (years)	72 (30-97)
Gender [no. (%)] of knees	
Female	186 (51.2%)
Male	177 (48.8%)
Mean (range) bodyweight (kg)	84 (51-168)
Mean (range) height (cm)	171 (125-223)
Mean body mass index (kg/m^2)	29
Compartment involved [no. (%) of knees]	
Varus	270 (74.4%)
Valgus	39 (10.7%)
Patellofemoral	33 (9.1%)
Two or more compartments	21 (5.8%)
No. (%) of knees with radiographic severity of grades 2 or 3	309 (85.1%)

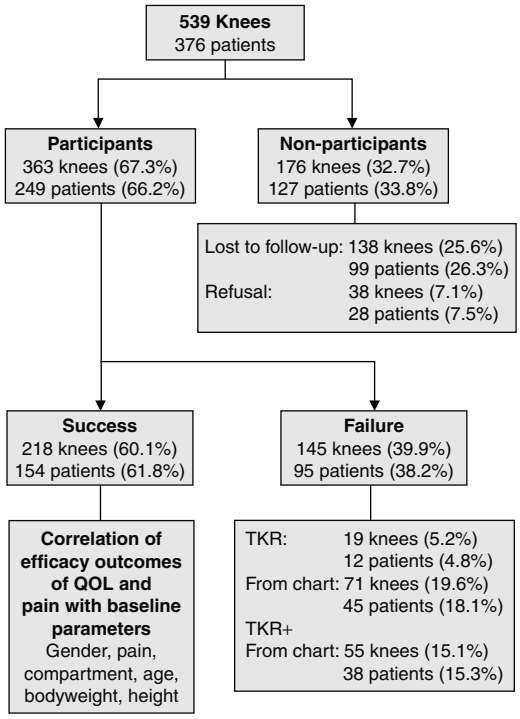

Fig. 1. Study design showing participants and non-participants, and therapeutic successes [lack of total knee replacement (TKR) or other significant intervention] and failures. Numbers of knees and patients are shown. **QOL** = quality of life.

Baseline patient characteristics are summarised in table I. A total of 51.2% of the knees belonged to women and 48.8% belonged to men. Among the successes, 55% were men and 45% were women; among the failures, 54.5% were men and 45.5% were women. The patients ranged in age from 30 to 97 years, with a mean value of 72 ± 11 years; the mean age was higher in failures than successes (74.8 ± 10.6 *vs* 70.2 ± 10.9 years, respectively). The mean height and bodyweight for all cases were 167.6 ± 12.2cm and 83.5 ± 19.0kg, respectively, with no significant differences between the successes and failures for either parameter.

X-ray analysis revealed that the compartment involved was varus in 74.4% of the knees analysed, valgus in 10.7%, and patellofemoral (PTF) in 9.1%, and in 5.8% of the cases, two or more compartments were involved. A somewhat higher percentage of failures had varus compartment involve-

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ment (79.3%) compared with successes (71.1%). Failures also had slightly lower valgus (9.7%), PTF (5.5%), and combined (5.5%) compartment involvement compared with successes (11.5%, 11.5% and 6% had valgus, PTF and combined compartment involvement, respectively).

In all knees, the mean degree of severity, on a scale of 0 to 3, was 2.62 ± 0.61 for the varus compartment, 2.51 ± 0.60 for the valgus compartment, and 1.97 ± 0.85 for the PTF compartment, indicating relatively severe disease for the population on the whole and confirming the initial clinical impression. Mean values for severity were higher in the failures for all compartments (2.78, 2.71 and 2.38 for varus, valgus and PTF involvement, respectively) compared with successes (2.5, 2.4 and 1.84 for varus, valgus and PTF involvement, respectively). Of all the x-rays analysed, 85.1% represented a severity of second or third degree; 90.4% of the failures and 81.7% of successes were of second or third degree severity.

Primary Efficacy Outcome: Success *vs* Failure

Of the 363 knees studied, 20.3% underwent TKR during the 6-month follow-up period, and a total of 145 (39.9%) were viewed as failures, having either undergone TKR or satisfied alternative criteria for therapeutic failure. Therefore, a total of 218 knees (60.1%) were judged as successfully treated and were assessed for outcomes regarding the parameters of QOL and pain (figure 1). Not all parameters were captured on every patient. A total of 196 knees were analysed for the QOL outcome, 198 knees were analysed for the outcome of pain on walking, 193 knees were analysed when the outcome was pain at rest, 194 knees were analysed when the outcome was pain under load, and 190 knees were analysed when the outcome was pain at night.

After treatment with Hyalgan®, an improvement in pain at rest was observed in 50.3% of cases, in pain on walking in 68.2%, in pain under load in 68.6%, and in pain at night in 51.6%. QOL scores were improved in 67.3% of the patients (table II). The correlations between these efficacy variables and potential baseline predictive factors were then determined using logistic regression analysis. The correlations for those relationships that proved significant by this analysis, either positively or negatively, are indicated in table III. Variables with no correlation values entered in the table were not correlated positively or negatively with the indicated outcomes. Assessment of the use of drugs to treat OA before and after treatment with Hyalgan® (see Appendix, question 7) indicated an improvement in terms of consumption or cessation of consumption in 20.7% of all cases evaluated (n = 213).

Quality of Life

Improvements in QOL were strongly correlated with knee compartment involvement and baseline pain on walking score (table III). Specifically, QOL showed greater improvement in cases in which knees were affected by OA in the PTF compartment and in cases in which higher baseline scores for pain on walking (score >5) were recorded. Valgus compartment involvement was also positively correlated with improved QOL, but to a lesser extent than PTF compartment. The association between the PTF compartment involvement and improvement in QOL also proved significant

Table II. Efficacy outcomes for cases judged as non-failures

Improvement measure	Efficacy outcomes[a]				
	quality of life (n = 196)	pain on walking (n = 198)	pain under load (n = 194)	pain at rest (n = 193)	pain at night (n = 190)
Cases improved (%)[b]	67.3	68.2	68.6	50.3	51.6
Mean improvement (score)	2.1	2.3	2.4	1.6	1.6

a Outcomes were calculated on an ordinal scale from 1 (best) to 10 (worst); scores were then reported as dichotomy variables (improved *vs* non-improved) based on the differences in scores before and after treatment.

b All efficacy outcomes were determined per knee treated; patients receiving treatment on two knees were contacted twice.

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Table III. Correlation between efficacy outcomes in patients judged as successes and potential predictive factors

Baseline variable	Correlation with efficacy outcomes[a, b]				
	quality of life	pain on walking	pain under load	pain at rest	pain at night
Gender					
Baseline pain	+0.5715		+0.8597		
Compartment					
Valgus	+0.5691	+0.9625	+0.2733		
Patellofemoral	+1.9062	+0.4594	+1.2021		
Severity					
Grade 2		+0.8012		+0.6751	+0.4252
Grade 3		+0.0864		+0.1486	-0.2079
Age				+0.4318	+0.1830
Bodyweight					
Height		+0.9805	+1.0255		
Body mass index					

a Efficacy outcome scores were calculated on an ordinal scale of 1 (best) to 10 (worst) and were knee-based.

b All correlations for which *r*-values are shown were significant by multivariate logistic regression analysis at a level of significance of 0.15; plus and minus signs indicate positive and negative correlations, respectively. Those outcomes with no entries were not significantly correlated with the indicated baseline variable.

(p = 0.012) by analysis using contingency tables. Thus, 91.7% of knees with PTF compartmental involvement improved, compared with 75.0% and 62.2% improvers with valgus and varus compartment involvement, respectively (figure 2a). Of those cases in which patients reported the greatest degree of pain on walking at baseline (score >5), 70.8% experienced an improvement in QOL score, but only 57.7% of those reporting a lesser degree of pain (score ≤5) experienced improvement in QOL (figure 2b).

Pain on Walking

Also shown in table III, improvement in pain on walking tended to be correlated with height, degree of radiographic disease severity, and compartment involvement. The taller patients (those >165cm), patients suffering from a grade 2 OA by x-ray, and those with disease affecting mainly the valgus compartment experienced the greatest improvement in pain on walking. PTF compartment involvement was also correlated with improvement in pain on walking, but to a lesser extent than valgus compartment improvement. More than 80% of cases with valgus compartment involvement improved, compared with 65.5% and 70.8% of those

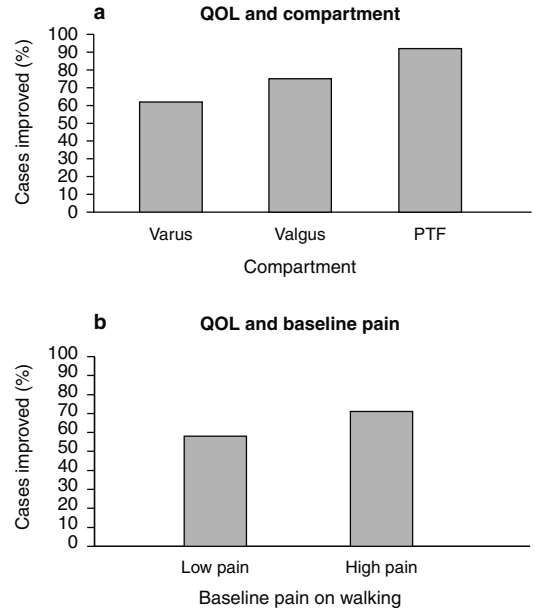

Fig. 2. Percentage of cases with improved QOL scores among therapeutic successes according to (**a**) varus, valgus or patellofemoral (PTF) compartment involvement and (**b**) baseline pain on walking score. Pain scores were based on an ordinal scale of 1 (best) to 10 (worst); low and high pain scores were ≤5 and >5, respectively.

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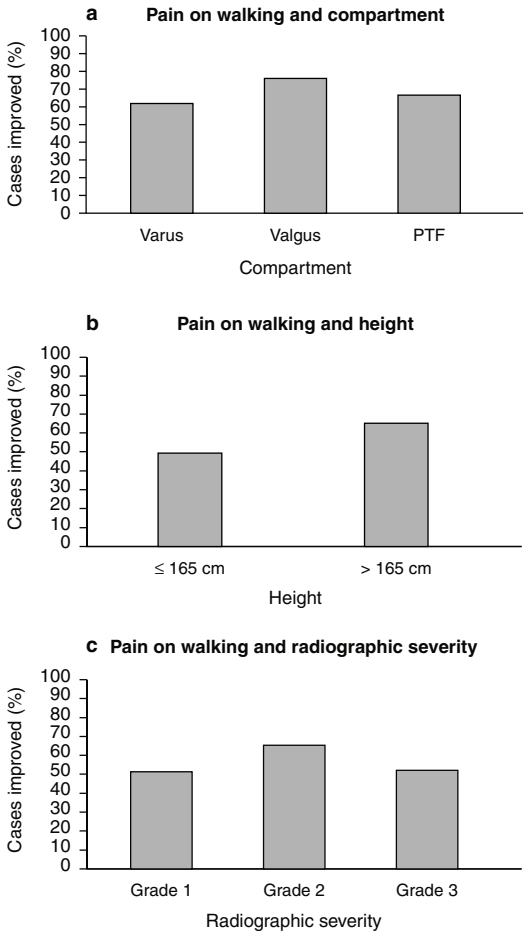

Fig. 3. Percentage of cases with improved scores for pain on walking among therapeutic successes according to (**a**) varus, valgus or patellofemoral (PTF) compartment involvement, (**b**) height (≤165cm or >165cm), or (**c**) radiographic disease severity (grade 1, 2 or 3). Pain scores were based on an ordinal scale of 1 (best) to 10 (worst); low and high pain scores were ≤5 and >5, respectively.

with varus and PTF disease (figure 3a). Improvement was noted in 78.1% of patients who were >165cm, compared with only 58.8% of those who were ≤165cm (figure 3b). When baseline severity of pain on walking was considered, the highest percentage of improvers in pain was noted in knees rated as grade 2 OA by x-ray (79.1%); improvement was seen in 61.5% and 62.9% of cases of grade 1 and grade 2 OA involvement, respectively (figure 3c). However, only the correlation with height was significant by contingency table analysis ($p = 0.004$).

Pain Under Load

The results indicated that the factor most positively related to improvement of pain under load was PTF compartment involvement, followed by greater height (>165cm) and a higher baseline score for pain (score >5) [table III]. Of cases with PTF compartment involvement, 83.3% were improvers, compared with improvement in 70.8% and 65.8% of cases with valgus and varus compartment involvement, respectively (figure 4a). In patients who reported a greater degree of pain at baseline (score >5), pain under load was improved in 72.4% but improvement was seen in only 57.1% of cases associated with lower baseline pain on walking (score ≤5) [figure 4b]. With regard to height, taller patients (>165cm) had a higher percentage of improvers (77.1%*vs* 60.2% for taller *vs* shorter patients, respectively) [figure 4c]. Contingency table analysis indicated that correlation with improvement in pain under load was significant for the baseline variables of pain on walking ($p = 0.047$) and height ($p = 0.011$).

Pain at Rest/Pain at Night

Multivariate logistic analysis indicated that improvements in pain at rest and at night were both correlated with grade 2 OA severity and age <70 years, but the predictive value of the baseline variables was not as strong for these outcomes as that for improvements in QOL, pain on walking or pain under load (table III). A total of 60.3% of the patients with grade 2 OA severity experienced an improvement in pain at rest, compared with only 45% of patients with either grade 1 or grade 3 severity, respectively. Similarly, improvement in pain at night was noted in 61.5% of cases with an x-ray severity of grade 2, whereas only 45% of cases with baseline severity of grade 3 showed

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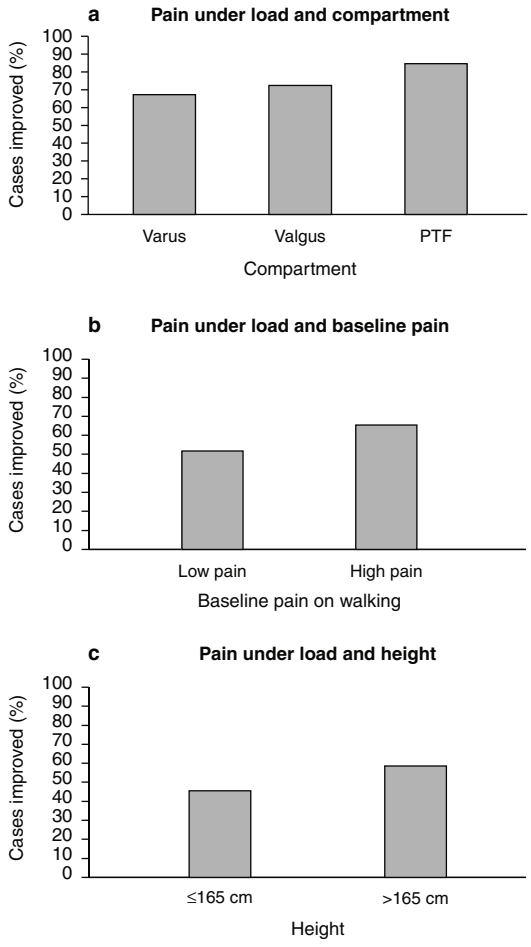

Fig. 4. Percentage of cases with improved scores for pain under load among therapeutic successes according to (**a**) varus, valgus or patellofemoral (PTF) compartment involvement, (**b**) baseline pain on walking, or (**c**) height (≤165cm or >165cm). Pain scores were based on an ordinal scale of 1 (best) to 10 (worst); low and high pain scores were ≤5 and >5, respectively.

improvement in this parameter. This was indicated by a negative correlation between improvement in pain at night and grade 3 disease severity (table III).

With regard to age, 57.3% and 55.8% of patients under 70 years of age experienced improvement in pain at rest and at night, respectively, compared with only 45.8% and 48.7% of patients 70 years or older, respectively. However, this trend towards a correlation with efficacy outcome was not significant by contingency table analysis.

Discussion

Although the effectiveness of a single course of Hyalgan® has been confirmed in a number of randomised, controlled and non-blinded clinical trials,[6,8,9,11] the environment of a clinical trial with inclusion and exclusion criteria may not accurately mimic the situations encountered in clinical practice. For example, Altman and Moskowitz [8] and Huskisson and Donnelly[9] restricted enrolment of patients to those with Kellgren-Lawrence grade 2 or 3, excluding patients with very mild and end-stage disease. Furthermore, the average age of patients in these controlled clinical trials was 64 and 66 years, respectively, in contrast to patients in the present study, who averaged 72 years of age. In these controlled clinical trials, rescue medication for pain in saline control and Hyalgan®-treated groups was restricted to simple analgesics [paracetamol (acetaminophen)], unlike a clinical practice in which patients may be taking a number of prescription and over-the-counter pain medications. Although uncontrolled, the data in this retrospective study augment the observations from randomised, controlled clinical trials and provide important insight into the effectiveness of Hyalgan® in a clinical practice. Hyalgan® provided a clear therapeutic benefit to the elderly population studied, as indicated by the absence of significant therapeutic intervention during a 6-month follow-up in the majority of patients, all of whom were candidates for TKR at the outset of treatment. In addition, the therapy demonstrated an excellent safety profile with no serious adverse events reported in this patient population. This is in significant contrast to other medications used to treat the pain associated with OA of the knee in this patient population.[17]

In this study, the previous clinical presentation and x-ray had categorised these patients as candi-

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dates for TKR prior to Hyalgan® treatment, and this assessment was confirmed by a review of the charts and x-rays by an independent clinician. Therefore, the finding that only 20.3% of cases underwent surgery during the prescribed follow-up period was impressive and suggested that Hyalgan® treatment may have delayed surgery in up to 80% of cases. Data from randomised, controlled trials suggest that a single course of Hyalgan® therapy may be effective for as long as 1 year in some patients.[6,18] Further study in the clinical practice setting, comprising follow-up periods of longer duration, will be necessary to determine whether a single course of Hyalgan® can continue to delay surgery beyond 6 months in a significant proportion of patients with moderate to severe OA.

Outcomes related to QOL and pain relief were evaluated in greater detail in patients who did not receive major intervention therapy during the follow-up period. Although these measurements were based on retrospective patient reporting, which has been associated with an increase in patients' perceptions of relief over time,[19] it is important to note that these outcomes were not considered as the primary measure of therapeutic effectiveness. The primary measure of effectiveness was the objective assessment, based on patient charts, of whether there had been TKR or other significant intervention. Rather, these pain measures were used in an effort to identify baseline variables that might be correlated with greater or lesser success with regard to pain relief. There is no reason to assume that there would have been any systematic bias in reporting on the part of patients with certain baseline characteristics rather than others.

The questionnaire results indicated that QOL, pain on walking, and pain under load improved in the large majority of patients, whereas only slightly more than half of patients showed improvement in scores for pain at rest or at night. Pain at rest and night are most often considered symptoms of more advanced disease and are perhaps more difficult to manage clinically with analgesia. This may provide a basis for our observation that patients with more severe disease (grade 3), as determined by x-ray, did not exhibit as great an improvement in pain scores as those with second-degree severity. This finding was in agreement with that of Lussier et al.[13] in a retrospective study of Hylan G-F 20, in which early- or intermediate-stage patients had significantly better efficacy outcomes than did those with end-stage (grade 4) disease.

Correlation of QOL scores and pain relief with baseline measurements indicated several factors that were predictive of treatment success: (i) improvements in QOL were positively correlated with higher baseline pain scores and PTF compartment involvement; (ii) improvement in pain on walking was positively correlated with valgus compartment involvement, second-degree disease severity by x-ray, and greater height (>165cm); (iii) pain under load showed greatest improvement in patients with PTF compartment involvement and greater height; (iv) pain at rest showed greatest improvement in patients with second-degree disease severity and age <70 years; (v) pain at night was positively correlated with age <70 years and was negatively correlated with greater disease severity (grade 3). Because the patients with PTF compartment tended to have a less severe grade of OA on x-ray, it is unclear whether the correlations with PTF compartment involvement are truly anatomical or directly related to the severity of the disease. Interestingly, despite findings that prevalence and progression of OA of the knee are correlated with bodyweight and BMI,[20] neither of these parameters was correlated either positively or negatively with the response to therapy with Hyalgan®. Although older patients and those with the most severe disease did somewhat more poorly than younger patients with less severe disease, the overall improvement seen in this elderly population with relatively severe disease indicated that Hyalgan® is an effective treatment option for the majority of these patients.

On the basis of both logistic regression and contingency table analysis of all outcomes, the results indicated that patients with PTF compartment dis-

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ease and taller patients received the greatest benefit from a single course of treatment with Hyalgan®. The relationship between PTF compartment involvement and improvement with Hyalgan® contrasted with the Lussier et al.[13] report, in which no significant relationship was observed between knee compartment involvement and the effectiveness of therapy with hylan. However, as previously noted, our present positive correlation may also be related to the less severe disease associated with the PTF compartment.

Conclusion

This retrospective study of patients treated with a single course of Hyalgan® in a clinical practice indicated that treatment was effective in the majority of patients for preventing or delaying TKR or other major intervention therapy. This efficacy outcome was associated with an excellent safety profile, making this therapeutic modality a very important treatment option in this patient population. Moreover, the majority of patients who did not receive intervention therapy during the follow-up period experienced improvements in QOL scores and in pain on walking and under load. The greatest improvements were observed in taller patients and in those with PTF compartment disease.

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Appendix 1: Phone Survey Questions

For some questions, affirmative answers were followed up by additional questioning to establish types of intervention or medication, dosages, duration, etc.

1. Would you be willing to participate in this survey?

2. Did you receive the full course of five injections of Hyalgan®?

3. Have you received any medication or therapy other than that for your treated knee that was for general pain relief or may have significantly altered your mobility (cast, hip replacement, etc.) in the past 6 months following Hyalgan® therapy?

4. Have you requested and received any intervention therapy for pain in the treated knee from the Florida Knee and Orthopedic Center or any other physician in the 6 months following Hyalgan® therapy?

5. Have you taken prescription medication for pain of the treated knee before Hyalgan® therapy?

6. Have you taken prescription medication for pain of the treated knee after Hyalgan® therapy for the treated knee?

7. If you have taken or are taking prescription medication in the 6 months following Hyalgan® therapy, is it more, less or the same as before you received treatment?

8. Have you taken or are you presently taking non-prescription or dietary supplements for the relief of pain or inflammation [Tylenol®, paracetamol (acetaminophen), aspirin, Advil®, ibuprofen, topical analgesics, chondroitin sulphate, glucosamine, etc.] during the 6 months after Hyalgan® therapy?

9. Have you taken or are you presently taking non-prescription or dietary supplements for general pain or inflammation, or the relief of symptoms due to injuries or disease other than the treated knee [Tylenol®, paracetamol (acetaminophen), aspirin, Advil®, ibuprofen, topical analgesics, chondroitin sulphate, glucosamine, etc.] during the 6 months following Hyalgan® therapy?

10. Have you used any device (e.g. wheelchair, cane, walker, crutch) to assist you in walking or maintaining mobility because of the osteoarthritis of the treated knee prior to Hyalgan® therapy?

11. Are you presently using or have used a device (e.g. wheelchair, cane, walker, crutch) to assist you in walking or maintaining mobility because of the osteoarthritis of the treated knee in the 6 months since Hyalgan® therapy?

12. On a scale of 1 to 10 how would you rank your quality of life relative to pain and mobility associated with your osteoarthritis in the treated knee prior to receiving Hyalgan® therapy (1 = highest quality, total independence; 10 = lowest quality, immobile and very dependent)?

13. On a scale of 1 to 10 how would you rank your quality of life relative to pain and mobility associated with your osteoarthritis in the treated knee prior to receiving Hyalgan® therapy (1 = highest quality, total independence; 10 = lowest quality, immobile and very dependent)?

14. On a scale of 1 to 10 how would you rank your pain at rest, when walking, with a load and at night associated with the treated knee both before and 6 months after Hyalgan® therapy (1 = no pain, 10 = unbearable pain)?

15. How would you rank the effectiveness of your Hyalgan® therapy (excellent, good, moderate, no benefit/ineffective, made OA worse)?

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