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## Hyaluronic Acid for the Treatment of Knee Osteoarthritis

### Long-Term Outcomes from a Naturalistic Primary Care Experience

**ABSTRACT**

Petrella RJ: Hyaluronic acid for the treatment of knee osteoarthritis: Long-term outcomes from a naturalistic primary care experience. *Am J Phys Med Rehabil* 2005;84:278–283.

**Objective:** Intraarticular hyaluronic acid is indicated for patients with osteoarthritis of the knee. However, clinical experience, especially efficacy and adverse events, with repeated injection series in the long term are limited.

**Design:** Patients were referred to a large primary care center for management of osteoarthritis of the knee. All were naive to intraarticular hyaluronic acid therapy and met our entry criteria, including resting visual analog scale pain of >45 mm, radiographic confirmation of unilateral knee grade 1–3 osteoarthritis, and willingness to receive intraarticular therapy. Patients received a three–intraarticular injection series with Suplasyn (10 mg/ml, 2-ml injection) over 3 wks. Patients were instructed to return for consideration of repeat injection series based on their perception of pain restricting daily activity and a resumption of severity similar to their initial presentation. This prospective naturalistic cohort was followed for 6.7 yrs. Patients completed baseline assessment of rest and walking visual analog scale pain (primary efficacy variable), completed a 5-point categorical global satisfaction score, and recorded adverse events and concomitant therapeutic modality use at each study visit. Patients returned for consideration of a repeat injection series based on their perception of symptom severity and were eligible if their resting visual analog scale pain was >45 mm. The three-injection series and data collection were repeated, and again, patients were given similar instructions regarding consideration of a third injection series.

**Results:** Of 897 referral patients, 537 (mean age, 68 ± 8 yrs; mean duration of symptoms, 7.4 ± 4.1 yrs) met our criteria, and only 21 patients did not return for a second injection series. The mean time between first and second series was 27 ± 7 wks. The change in walking visual analog scale pain was significantly improved from baseline after the first series (81.3%,  $P < 0.001$ ) and second series (86.7%,  $P < 0.0001$ ). Similarly, resting visual analog scale pain was significantly decreased from baseline after the first ( $P < 0.001$ ) and second ( $P < 0.001$ ) series, and patient satisfaction was significantly improved with each injection series ( $P < 0.03$  and  $P < 0.01$ ). Very few adverse events were recorded and were limited to local pain and swelling. Use of concomitant therapeutic modalities at presentation for a second injection series included: nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 medications (37%), acetaminophen (31%), oral nutraceuticals (12%), and physical therapy and bracing (12%).

**Conclusions:** Intraarticular hyaluronic acid injections were highly effective in improving resting and walking pain in patients with osteoarthritis of the knee on a first and a second treatment series. Duration of symptom control was about 6 mos, and the therapy was highly satisfactory to patients and was associated with very few local adverse events and limited use of concomitant therapeutic modalities. These data support the potential role of intraarticular hyaluronic acid as an effective long-term therapeutic option for patients with osteoarthritis of the knee.

**Key Words:** Hyaluronic Acid, Knee Osteoarthritis, Longitudinal Naturalistic Sample

**H**yaluronic acid (HA) is an unbranched, high-molecular weight polysaccharide distributed throughout the body, especially as a major component of the synovial fluid and of cartilage. The primary role of the HA in synovial fluid and cartilage is to maintain the viscoelastic structural and functional characteristics of the articular matrix. Osteoarthritis is the result of mechanical and biological events that destabilize the normal degradation and synthesis of articular cartilage<sup>1</sup> and is characterized by a decrease in the concentration and molecular weight of HA, which in turn may contribute to the hallmark signs of pain and loss of function in weightbearing joints such as the knee.<sup>2</sup> Hence, intraarticular viscosupplementation with HA may restore the concentration and molecular weight characteristics in the articular matrix, resulting in improved pain control and function.

Intraarticular HA is indicated currently for use in patients who may not have responded to a program of nonpharmacologic therapy and pain control with analgesics including acetaminophen.<sup>3</sup> Clinical trials of intraarticular HA preparations have shown pain relief in HA-treated patients significantly greater than in those who were injected with placebo<sup>4-7</sup> and comparable with or superior to intraarticular corticosteroids.<sup>8</sup> Although pain relief is achieved more slowly with HA preparations than with intraarticular corticosteroid injections, the effect may last considerably longer.<sup>9</sup> Similarly, intraarticular HA has shown comparable improvement in pain with oral anti-inflammatory preparations.<sup>9</sup> This latter finding may be especially advantageous in patients in whom nonselective anti-inflammatories and cyclooxygenase-specific inhibitors are contraindicated or in those who have experienced either a lack of efficacy or other adverse events.

Given the chronic nature of osteoarthritis, the potential utility of HA is currently limited by the paucity of data concerning not only the effectiveness in the short term<sup>10</sup> but the effectiveness of long-term multiple courses of intraarticular HA therapy<sup>11</sup> in a naturalistic, usual care setting. In one open-labeled, multicenter trial investigating the use of HA in 108 patients over a 12-mo period,<sup>12</sup> 59 completed a first cycle and a 12-mo follow-up, 14 began a new treatment cycle after 4-8 mos, and six patients completed a second follow-up cycle. A total of 35 patients (32%) withdrew before the end of the 12-mo period secondary to adverse events, noncompliance, patient refusal, loss to follow-up, and protocol evaluation. It was observed that patients (only six) who required a second treatment cycle showed further amelioration of symptoms. Measures of knee function were also shown to improve at follow-up, as did global effi-

cacy evaluations from both the patients and investigators. We are unaware of any other published studies that have prospectively observed patients who were administered HA for treatment of knee osteoarthritis in routine clinical practice. Hence, the purpose of this study was to evaluate both clinical and functional outcomes, including adverse events and the use of concomitant medications in patients who received more than one series of intraarticular viscosupplementation with HA (Suplasyn) for knee osteoarthritis in routine clinical practice.

## METHODS

### Subjects

Patients were recruited consecutively from a large primary care referral center (Canadian Centre for Activity and Aging) for assessment of knee osteoarthritis. From this referral source, a cohort of 537 patients from a total referral group of 897 patients with unilateral osteoarthritis of the knee was observed after an initial series of three intraarticular HA injections with Suplasyn (10 mg/ml, 2.0 ml). Although patients could have osteoarthritis in the contralateral knee, it could not be functionally limiting or have pain exceeding the index knee as described below. At entry, all patients had, in the index knee, radiographic evidence of grade 1-3 medial compartment osteoarthritis,<sup>13</sup> did not exhibit nonarthritis-related disease, had no regular

**Objectives:** On completion of this article, the reader should be able to (1) understand the mechanism by which intraarticular hyaluronic acid improves clinical and functional outcomes in patients with osteoarthritis of the knee, (2) understand the advantages of intraarticular hyaluronic acid over other conventional treatments in osteoarthritis of the knee, and (3) understand the impact of chronic intraarticular hyaluronic acid on clinical and functional outcomes in osteoarthritis of the knee.

**Level:** Advanced.

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(>3 days/wk) concomitant nonsteroidal anti-inflammatory use, had no previous intraarticular HA or glucocorticoid injections, were not regularly using nutraceutical osteoarthritis products (including glucosamine sulfate or chondroitin sulfate), and all gave consent as approved by the University of Western Ontario ethics review board.

### Assessment

Baseline assessment included demographic data (age, sex, body mass index, comorbidities, and concomitant medications). All patients qualified for intraarticular HA injection based on history of unilateral knee pain and disability, radiographic evidence of osteoarthritis (as above), and a non-weightbearing, visual analog scale (VAS) score of seated-rest pain of at least 45 out of 100 mm. Outcome measures included those recommended previously.<sup>14,15</sup> The primary efficacy variable was improvement in self-paced 40-m walking VAS pain score.<sup>6</sup> Secondary outcomes included improvement in VAS score of seated-rest pain, patient global satisfaction using a 5-point numerical scale weighted from completely satisfied<sup>5</sup> to completely unsatisfied,<sup>1</sup> presence of adverse events, and concomitant medications.

All assessments were repeated by the same independent technician. This approach was repeated before a third HA series.

### Intervention

Suplasyn is a solution of HA of 500–730 kDa indicated for intraarticular injection for knee osteoarthritis. It is currently available and approved in >20 countries worldwide. Two milliliters of intraarticular HA at a concentration of 10 mg/ml was injected under sterile field using a medial approach. No anesthetics were used either topically or intra-articularly. Each injection (in the series of three injections) was performed 1 wk apart ( $\pm 2$  days) by an experienced clinician. All injections were initiated after baseline assessments of VAS and global satisfaction, which were performed by an independent technician. Return for consideration of a subsequent intraarticular HA series was based on patient request triggered by pain and disability interfering with activities of daily living and perception of similar symptoms to those experienced with their first presentation. This approach was aimed at replicating the usual clinical practice experience. All return visit interval dates were screened for extraneous influences on duration, including cost of HA and distance to travel to the clinical site, among others, and were not a factor in any follow-up visit. Patients were free to seek additional therapeutic modalities, including physical therapy and analgesics (including nonsteroidal anti-inflammatory drugs) but not intraarticular ther-

**TABLE 1** Baseline characteristics

Data Fields	Data Collected
No. of patients	537
Mean age of patients, yrs	68 $\pm$ 8
BMI, mean $\pm$ SD	27.2 $\pm$ 2.1
Duration of symptoms in years, mean $\pm$ SD	7.4 $\pm$ 4.1
BMI, body mass index (kg/m <sup>2</sup> ).	

apies before their presentation for a second series of HA injections. All concomitant treatments were recorded. Qualification for a second series of HA injections also required a VAS score of seated-rest pain of at least 45 mm and the absence of other intraarticular treatments but could include other ongoing therapeutic modalities.

Suplasyn was purchased by study participants and was not subsidized by the manufacturer. Few received independent reimbursement by a third-party insurer. Individuals who were reimbursed did not differ in demographics, primary or secondary outcomes, or treatment interval from the total cohort.

### Statistical Analysis

Analysis of variance with repeated measures and  $\chi^2$  test were used to test for differences from baseline characteristics of the group among the primary and secondary outcomes at each injection series interval. Analyses were conducted using Sigma Stat (SPSS, Chicago, IL) and Microsoft Excel (Microsoft, Redmond, WA). Changes in VAS were calculated in percentages of improvement from baseline. Significance was established at  $P < 0.05$ .

## RESULTS

### Subject Characteristics

Recruitment of participants was conducted over 6.7 yrs. The study population of 537 patients was extracted from a total referral group of 897 patients with unilateral knee osteoarthritis meeting our entry criteria over that time frame. The study population did not differ in baseline characteristics from the total referral group. Reasons for nonparticipation included referral from a distant center, request for an alternate HA product, and refusal to provide consent for intraarticular therapy. Study population baseline demographics are given in Table 1. Fifty-eight percent of subjects presented with right knee osteoarthritis. Only 21 of 537 patients failed to return during the follow-up period; however, all were contacted (personally or through family) during the follow-up period. Of these, eight patients had entered a retirement or

**TABLE 2** Percentage improvement in visual analog scale scores for walking pain with first and second hyaluronic acid series

First Series		Second Series	
Visit	Assessment <sup>a</sup>	Visit	Assessment <sup>a</sup>
1		5	10.3
2	22.7 ( $P < 0.04$ )	6	25.3 ( $P < 0.01$ )
3	36.1 ( $P < 0.01$ )	7	51.4 ( $P < 0.001$ )
4	81.3 ( $P < 0.001$ )	8	86.7 ( $P < 0.001$ )
		9	12.1

<sup>a</sup>Average percentage of improvement from baseline visual analog scale scores for walking pain.

nursing home or moved away, six patients had undergone arthroplasty, and three patients claimed to have had significant adverse effect of the injection series and failed to return. Two patients died during follow-up from unrelated causes, and two patients failed to have resumption of symptoms during the follow-up period.

The mean age of patients was  $68 \pm 8$  yrs, mean body mass index was  $27.2 \pm 2.1$ , and 65% of the patients were women. The mean duration of osteoarthritis symptoms was  $7.4 \pm 4.1$  yrs. Of the 537 patients, 516 patients returned for second and third injection series during the follow-up phase. Seventy-seven percent of patients described one or more concomitant medical problems at baseline. The most prevalent problems were hypertension (26%), gastrointestinal disorders (17%), type-2 diabetes (11%), and other osteoarthritis (8%). Fifty-eight percent of patients regularly used acetaminophen, 53% regularly used nonsteroidal anti-inflammatory drugs/cyclooxygenase-2, 46% regularly used nutraceuticals, and 23% used physical therapy or bracing. Concomitant therapies had no impact on outcomes when controlled for in the analysis. The mean time between the first and second series course of Suplasyn was  $27 \pm 7$  wks (range, 12–84 wks) and  $29 \pm 15$  wks (range 9–112 wks) between the second and third HA series.

### Primary Outcome

The primary efficacy outcome was percentage of improvement from baseline in walking VAS pain. The significant improvements in walking VAS pain were seen at visit 2 (22.7%,  $P < 0.04$ ), visit 3 (36.1%,  $P < 0.01$ ), and visit 4 (81.3%,  $P < 0.001$ ) with the first HA series (Table 2, Fig. 1). No significant difference between baseline and visit 1 ( $P < 0.10$ ) and visit 5 ( $P < 0.07$ ; return visit for second HA series) was observed.

On presentation for a second HA series, a significant improvement in walking VAS pain at visit

6 (25.3%,  $P < 0.01$ ), visit 7 (51.4%,  $P < 0.001$ ), and visit 8 (86.7%,  $P < 0.0001$ ) was observed from visit 5 (Table 2, Fig. 1). Furthermore, a significant improvement between visit 3 and visit 7 (36.1% vs. 51.4%,  $P < 0.001$ ) and visit 4 and visit 8 (81.3% vs. 86.7%,  $P < 0.03$ ) was observed with the second HA series (Table 2). Visit 9 represented a return for a third HA series. There was a significantly greater ( $P < 0.001$ ) improvement from visit 5 to visit 9 (10.3% vs. 12.1%) for these patients (Fig. 1).

### Secondary Outcomes

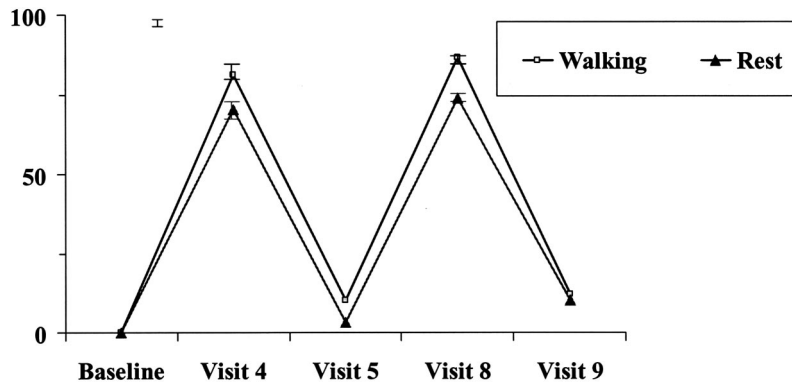
Resting VAS pain was significantly improved from baseline to visit 2 (17.2%,  $P < 0.02$ ), visit 3 (26.3%,  $P < 0.01$ ), and visit 4 (70.4%,  $P < 0.006$ ). There were similar improvements from visit 5 (return for second HA series) for visits 6, 7, and 8 (Table 3, Fig. 1). No difference between visits 5 and 9 was observed.

Patient satisfaction with the first HA series (at visit 4) was  $4.68 \pm 0.6$  ( $P < 0.03$ ), and  $4.83 \pm 0.08$  ( $P < 0.01$ ) after the second series (at visit 8). There were no systemic adverse events reported. Local adverse events including pain and swelling at the injection site were observed in 1.48% and 1.32% of injections with the first and second HA series, respectively. Only three adverse events were reported among those who presented for a third HA series.

Forty-one percent of patients returning for a second HA series reported regular (three or more times per week) concomitant use of alternate knee osteoarthritis therapeutic modalities. The most prevalent modalities included nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors (37%), acetaminophen (31%), nutraceuticals (12%), and physical therapy or bracing (12%). There was no significant difference between the use of concomitant therapeutic modalities for those at the second or third HA series. No other intraarticular injections were performed on any of the study patients observed at the second or third HA series.

### DISCUSSION

This large cohort of 537 patients with knee osteoarthritis, who were naive to intraarticular injection with HA, received at least two successive series of intraarticular injections with 2.0 ml (10 mg/ml) of Suplasyn and demonstrated improved pain symptoms at rest and during walking with each treatment series. HA injections were highly satisfactory to patients with each HA series and included a very low rate of local adverse events and a very high retention rate. Patients returned for second and third HA series based on their own perception of restricted function and pain at a treatment interval of 27 wks, and they used relatively few alternate therapeutic modalities for os-



**FIGURE 1** Changes in walking and rest visual analog scale pain for first and second hyaluronic acid series.

teoarthritis. Hence, this representative sample from a naturalistic, usual care clinical setting demonstrated that the use of HA in osteoarthritis of the knee was effective and acceptable in relieving symptoms and in improving function with few local adverse events and little use of concomitant therapeutic modalities. These findings suggest that intraarticular HA may be an important treatment option for patients with osteoarthritis of the knee.

The effect of Suplasyn on activity-related pain seemed to be somewhat greater than the improvement in rest-mediated pain, which is similar to previous reports of shorter-term, randomized, clinical trials with this product.<sup>6</sup> This study directly addresses an acknowledged need for longer-term clinical experience with HA. The American College of Rheumatology<sup>3</sup> stated that “while clinical trials of intraarticular hyaluronan preparations seem to improve pain relief comparable with oral antiinflammatory preparations, these trials have been limited in the duration of observation, as well as experience with effectiveness of multiple courses of intraarticular hyaluronan therapy.”<sup>3</sup> In particular, it has been unclear whether repeated intraarticular series have further improved symptom control or whether this is associated with a

change in adverse event rates.<sup>11,12</sup> Hence, the present study shows for the first time that repeated intraarticular injections with a midrange molecular weight HA (Suplasyn) not only improved both rest and walking pain symptoms in patients with unilateral knee osteoarthritis for 27 wks, but that for walking pain in particular, the improvement seems to be even greater after a second HA series, with little need for alternate therapeutic modalities and very few adverse events. The long duration of follow-up (6.7 yrs), large cohort of patients who demonstrated few withdrawals, and a high degree of patient satisfaction are notable and should assist clinicians when generalizing these findings in discussion of therapeutic options with similar patients in their practice setting.

The duration of acceptable symptom control in this cohort ( $27 \pm 7$  wks; range, range of 12–84 wks), despite residence time of about 28 days,<sup>2</sup> suggests a possible disease-modifying influence of HA in osteoarthritis of the knee. Inclusion of imaging in the design of the current study may have corroborated this postulation. Future studies including more detailed joint space imaging could explore the effect of HA on osteoarthritis disease modification in the knee.

Clinical trial evidence for HA to date has been limited by a paucity of studies over a duration of 12 wks or studies in which multiple treatment cycles have been included. Hence, this study provides important usual care or naturalistic clinical practice data in this growing patient demographic. Further investigation with HA regarding the identification and targeting of specific patient characteristics associated with a longer duration of symptom control will be an important consideration for long-term management of knee osteoarthritis. It is clear in our study that most patients required more than one HA series during the course of their disease for symptom control. Hence, targeting patient-specific indicators may provide important information regarding

**TABLE 3** Percentage improvement in visual analog scale score for resting pain with first and second hyaluronic acid series

First Series		Second Series	
Visit	Assessment <sup>a</sup>	Visit	Assessment <sup>a</sup>
1		5	3.3
2	17.2 ( $P < 0.02$ )	6	20.3 ( $P < 0.02$ )
3	26.3 ( $P < 0.01$ )	7	31.6 ( $P < 0.01$ )
4	70.4 ( $P < 0.006$ )	8	73.8 ( $P < 0.001$ )
		9	10.1

<sup>a</sup>Average percentage of improvement from baseline in visual analog scale score for resting pain.

the duration of anticipated effects and effective concomitant therapeutic modalities—both of which could have important economic consequences. Furthermore, self-purchase of HA was not a deterrent to patients in our experience. Coupled with a high degree of patient satisfaction and symptom control over a long period, HA may be cost saving—an area also important for future investigation.

We utilized a widely available HA product with standard dosing and injection regimen. However, it is possible that alternate dosing regimens, perhaps utilizing alternate molecular weight HA or concentration of HA, could further effect these findings (including longer duration of effects); therefore, alternate dosing regimens should be investigated.

A limitation of this study includes the absence of a control group. A control could have determined the size of a placebo effect, which has been described as high as 80%.<sup>10</sup> Further, given that many patients purchased their own injections, this could have resulted in an even greater placebo effect than observed in clinical trials. However, it was the intention of this study to document the clinical changes of patients with osteoarthritis of the knee after intraarticular HA injection in a naturalistic, usual care setting. It would not be usual care practice to randomize patients who present for a specific therapeutic option, nor would it be appropriate to subject them to a placebo.

In summary, intraarticular HA therapy was effective in reducing walking and rest VAS pain with both first and second series of injections separated by approximately 6 mos. Improvement of pain on walking was significantly better after a second HA series than on the first series, which may support some disease modifying changes in knee joint function that require further investigation. Intraarticular HA injection was highly satisfactory among patients for both first and second series. Relatively few local adverse and no systemic adverse events were reported, suggesting that overall, HA therapy is an important therapeutic option for patients with knee osteoarthritis. Future studies regarding optimal dosing, concentration, and molecular weight options for long-term effect of HA in osteoarthritis of the knee and other weight-bearing joints are needed. Also, economic benefits of using this therapeutic option should be determined given the long-term clinical benefit and the reduced apparent need for alternative osteoarthritis-modifying therapies.

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