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ORIGINAL PAPER

Hyaluronic acid injections for osteoarthritis of the knee: predictors of successful treatment

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Abstract

Purpose This study aimed to identify patient and treatment factors that predict a favourable response to intra-articular hyaluronic acid (HA) treatment to better guide patient and treatment selection.

Methods This prospective, observational study evaluated patients with mild-to-moderate (Kellgren–Lawrence grades 1–3) primary knee osteoarthritis treated between March 2013 and May 2016. Patient function and pain scores were assessed by the Western Ontario and McMaster Universities Arthritis Index/Knee Injury and Osteoarthritis Outcome Score (WOMAC/KOOS) and visual analogue scale (VAS) surveys, with response to treatment defined according to the Osteoarthritis Research Society International (OARSI) 2004 criteria. Surveys were completed at each injection and three months post-treatment. Patients were followed an average of 27 months.

Results Of 102 patients, 57% had a positive response. Those at least twice as likely to respond were patients with grades 1–2 osteoarthritis or a positive response to the first injection and those who were ≥60 years. Gender, race, body mass index (BMI), smoking status, HA brand, and initial VAS and WOMAC/KOOS scores were not significant predictors of success. Mean time to arthroplasty following injection series was 11 months (30% of nonresponders, 12% of responders). The VAS strongly correlated with KOOS pain scores and successful outcomes.

Conclusion Patients with mild-to-moderate osteoarthritis (grades 1–2) and those responding positively to the first injection were twice as likely to respond positively to the injection series, as were patients ≥60 years. Patients who did not respond positively were more likely to proceed to arthroplasty. The VAS appears to be a reliable method of defining and monitoring treatment success. Judicious patient selection and counseling may improve outcomes associated with intra-articular HA injections.

Keywords Osteoarthritis · Knee · Hyaluronic acid · Injection · Viscosupplementation

Introduction

Intra-articular viscosupplementation has emerged as a common, albeit controversial, tool in the non-operative management of osteoarthritis (OA) of the knee. More than 14 million people in the USA, ~17% of individuals >45 years, are affected by knee OA [1–3]. Currently, hyaluronic acid (HA) injections account for 25% of treatment costs associated with non-operative care for knee OA—higher than any other treatment [4]. In 2012, Medicare spent US$207 million on HA products [5]. With an aging population and increasing scrutiny of medical costs, the importance of defining efficacious treatments for OA is paramount.

When lifestyle modification, bracing, physical therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs) fail to relieve osteoarthritic symptoms, intra-articular HA injections are often considered. In the osteoarthritic knee, synovial fluid viscosity and elasticity decline, as do concentrations of HA [6]. HA is responsible for maintaining synovial fluid viscosity, assisting in proteoglycan synthesis, modulating inflammatory and pain responses and preserving the cartilage matrix [7–10]. Thus, intra-articular viscosupplementation evolved in an attempt to restore the normal viscoelastic properties of the knee by stimulating HA synthesis and diminishing its degradation [9–12].

Although many studies have evaluated the efficacy and safety of viscosupplementation, the question remains: Who is the best candidate to receive the treatment? This study

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aimed to identify patient and treatment factors that predict a favourable response to intra-articular HA treatment. We theorised that individuals with less severe knee OA and fewer risk factors, such as younger age and lower body mass index (BMI), would experience better outcomes. We also theorised that improvement would be gradual but that those who responded initially to the injections would have a better response at follow-up. Finally, we theorised that those who responded positively to the injection series would be less likely to proceed to arthroplasty or do so on a delayed basis. To our knowledge, this is the first prospective study specifically designed to evaluate patient and treatment factors related to successful HA treatment.

Methods

This was a prospective, observational study designed to evaluate the predictors of successful knee OA treatment with intra-articular HA injections. Patients were enrolled between March 2013 and May 2016. Data were prospectively collected from medical records, surveys, and NSAID diaries at least one year after treatment. This study was approved and monitored by our Institutional Review Board. Informed consent was obtained from each individual before enrollment. A US$25 stipend was provided for each participant after final survey submission. Included patients were individuals ≥35 years presenting with knee pain and Kellgren–Lawrence (KL) grade 1–3 primary knee OA. All patients initially underwent a trial of physical therapy, NSAIDs if able, and occasional bracing before HA injection therapy. KL grade was determined by a single, blinded investigator (Table 1) [13]. Patients were excluded if they had previous intra-articular HA injections in the knee; a corticosteroid injection within the previous three months; post-traumatic OA or knee trauma requiring surgery (including ligament or meniscal tears); knee arthroscopy within the previous year; history of crystalline-induced, septic or rheumatoid arthritis; severe nonarthritic or bony pathology; neurogenic or vascular claudication. Therefore, this was a hyaluronic-naïve group with primary knee OA that had been treated non-operatively.

The primary outcome measures were the Western Ontario and McMaster Universities Arthritis Index/Knee Injury and Osteoarthritis Outcome Score (WOMAC/KOOS) and a standardised visual analogue scale (VAS), where patients rated their current pain ranging from 0 to 100 [14–16]. The WOMAC/KOOS survey consists of a global score and five subscales: pain, symptoms, functions of daily living, sports/recreation and quality of life (QoL). Response to treatment was defined according to the Osteoarthritis Research Society International (OARSI) 2004 criteria [17]. Treatment response was classified as a success if: (1) the patient had pain, symptoms or physical function subscale improvement of at least 50% and at least a 20-point improvement on the VAS; or (2) the patient had an improvement in two of the four KOOS categories of pain, symptoms, function or global WOMAC score of at least 20% and had a VAS improvement of at least 10 points. Surveys were completed at the first HA injection and each subsequent injection, with a follow-up survey mailed three months after the last injection in the series.

Independent variables for analysis included age, race, sex, BMI, smoking status, OA grade, brand of HA, initial KOOS and VAS scores and response to initial injection. A positive response to the initial injection was defined as at least a 10-point improvement in the VAS and either a > 50% increase in KOOS pain subscale or >10% increase in two of the three categories of pain, symptoms and function. The brand of sodium hyaluronate was physician preference; only three week regimens of Supartz, Synvisc or Euflexxa were used. Patients received viscosupplementation according to the manufacturer's direction, with one injection per week. Enrollment and injections were performed by three physician providers.

Statistical analysis

A sample size of 87 patients was calculated as required to detect an effect size of 0.30, with an alpha of 0.05 and a beta of 0.80, based on the combined results of a meta-analysis by Rutjes et al. [18]. Descriptive statistics and data analysis, including group comparisons, were calculated using Microsoft Excel® and IBM® SPSS® Statistics version 22.0 for Mac. Response data were analysed using nonparametric Pearson chi-square test for nominal categories (gender, race, smoking status, first injection response and proceeding to arthroplasty), and Kendall's tau coefficient for ordinal data (OA stages). Independent sample t test was used to compare means between those who did and did no responded positively for age, BMI, VAS and KOOS scores. A Bonferroni correction was applied to these multiple t tests, which rendered a significant p value as $p \leq 0.002$. The association between the VAS and KOOS pain scores was assessed by Pearson correlation; Spearman's rho was used to assess the association between

Table 1 Kellgren–Lawrence (KL) radiographic classification of knee osteoarthritis

KL grade	Radiographic description
0	No osteophytes, normal joint space
1	Possible osteophytes, doubtful joint-space narrowing
2	Definite osteophytes, possible joint-space narrowing
3	Moderate osteophytes and sclerosis, definite joint-space narrowing
4	Large osteophytes with marked joint-space narrowing, sclerosis, deformity

change in VAS score for those who responded to the first injection and those who responded overall to treatment.

Results

Three hundred patients were screened for inclusion; 128 were enrolled. Of the 172 patients excluded, 157 met exclusion criteria, most commonly for a previous HA injection trial, a corticosteroid injection <three months, or post-traumatic OA. Fifteen patients declined participation. After enrollment, six patients withdrew from the study and/or HA treatment prior to completion: two for injection-related pain and four for uncited reasons. Three patients were removed secondary to surgical intervention within the immediate follow-up period: two for arthroscopic meniscectomies, and one for a total knee arthroplasty (TKA). Seventeen patients failed to complete all required surveys or were lost to follow-up. We analysed the 102 patients that remained (Fig. 1). Mean age was 60 years (range 35–94), 72% were women and mean BMI was 33. Twenty-six patients (25%) had KL grade 1 OA, 32 (31%) grade 2, and 44 (43%) grade 3. Eleven patients received Supartz, 19 received Synvisc and 72 received Euflexxa.

Of the 102 patients analysed, 58 (57%) met criteria for successful response to HA injection series (Fig. 1). Patients with grade 1 or 2 OA were 2.2 times more likely to respond to the injections than those with grade 3 OA ($p = 0.001$, Phi = −0.400). Those who responded positively to the first injection of the series were 2.3 times more likely to have a positive response at follow-up: 78% versus 35% ($p = 0.001$, Phi = 0.435). Initial KOOS and VAS scores, race, sex, BMI, smoking status and brand of injection had no effect on response to treatment. For grade 2 alone, patients >60 years were approximately twice as likely to respond positively than patients <60 years ($p = 0.009$, Phi = 0.465).

Those who did and did not respond successfully had statistically similar initial VAS and KOOS scores after Bonferroni analysis at the initial and second injections (Table 2). For those who responded positively, there was a significant change in VAS score between the first (mean = 6.1) and second (mean = 4.4) visits ($p = 0.048$) and between the second injection and follow-up (mean = 2.4, $p = 0.001$), indicating that pain relief improved gradually throughout the treatment period (Fig. 2). At final follow-up, there was a strong, significant difference in both absolute and percent change from baseline for all KOOS subscales among those who responded positively (Table 3; Figs. 3 and 4).

Patients were followed for an average of 27 months (range 12–50). Twenty patients received knee arthroplasty: one unicompartmental and 19 TKA; six patients underwent partial meniscectomies. Thirteen of those who did not respond positively to the injection series received an arthroplasty (30%), compared with seven patients who did respond (12%) ($p = 0.028$). Those who did not respond to treatment received their arthroplasty at a mean of ten months postinjection, while those who did respond received their arthroplasty at 13.4 months on average ($p = 0.185$). While NSAID usage appeared to decline in the positive-response group, definitive conclusions could not be drawn because of incomplete records. Four patients had complications related to therapy: pain at the injection site, swelling, redness and bruising; two of these patients withdrew from treatment because of pain related to the injections.

There was a strong inverse association between VAS and KOOS pain scores from the beginning to the end of treatment ($r = -0.77$), and at each time point ($r = -0.64$, -0.72, and -0.82.) Change in VAS also strongly correlated with response to first injection ($r = 0.416$) and with successful treatment ($r = 0.69$). The coefficient of determination (r^2) for a model using the VAS to predict KOOS pain subscale was 0.59.

Discussion

HA injections remain a widely used yet controversial treatment method for managing knee OA. In our study, 57% of patients had a successful response to HA therapy based on the

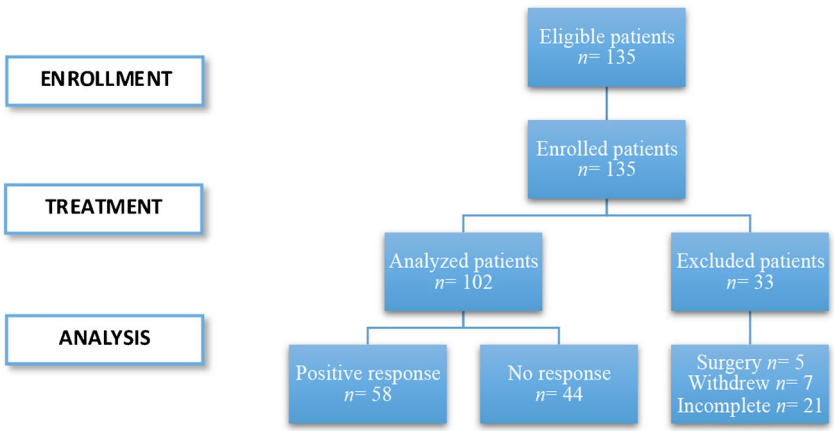

Fig. 1 Eligible, enrolled, treated and analysed participants

Table 2 Patient characteristics according to success of treatment with hyaluronic acid

	Positive response $N = 58$ (57%)		No response $N = 44$ (43%)		P value
Age	61	(1.23)	59	(1.56)	0.436
Sex					
Male	16	(55)	13	(45)	0.830
Female	42	(58)	31	(42)	
BMI	33.2	(0.82)	332	(126)	0.962
Smoking status					
Nonsmoker	51	(57)	39	(43)	0.914
Smoker	7	(58)	5	(42)	
Race					
White	48	(58)	35	(42)	0.683
Black	10	(53)	9	(47)	
OA grade					
I	22	(85)	4	(15)	
11	21	(66)	11	(34)	**0.001**
III	15		29	(66)	
1st injection response					
Yes	40	(78)	11	(22)	**0.001**
No	18		33	(65)	
Proceeded to arthroplasty					
Yes	7	(12)	13	(30)	**0.028**
No	51	(88)	31	(70)	

Age and body mass index (BMI) are mean and standard errors with t test probabilities; Smoking status, race, osteoarthritis (OA) grade, response to first injection and proceeding to arthroplasty are presented as frequency and percent; Kendall's tau coefficient p value is provided for OA grade; chi-square p values are provided for the remaining variables

Bolded data indicate significant difference

2004 OARSI criteria. Defining successful response to HA treatment is a challenge, which makes interpreting the literature difficult. Numerous studies and meta-analyses have examined the therapeutic effects of HA, with mixed results [18–23]. Large meta-analyses by Wang et al. [21] and Bellamy et al. [22] found marked improvement in pain scores, physical function and patient-assessed global outcome scores. A more recent review from the US Centers for Medicare and Medicaid Services by the Agency for Healthcare Research and Quality found improved function, QoL and potentially delayed TKA, particularly for those >65 [24]. However, there is debate over what constitutes a minimal clinically important difference [25]. Rutjes et al. [18] identified a significant, but clinically irrelevant, effect in their meta-analysis.

Because of these mixed reviews, it has been difficult to establish clinical practice guidelines, and several societies have changed their positions [19]. The American Academy of Orthopedic Surgeons (AAOS) initially viewed HA as a reasonable treatment option for knee OA, but in 2013, the AAOS revised its stance and now recommends against its use [26]. The American College of Rheumatology and OARSI initially endorsed its use but are now uncertain [27–29]. The American Medical Society for Sports Medicine and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis performed their own reviews and continue to recommend its use [30, 31].

Based on this study's subgroup analysis, patients with mild to moderate OA are more likely to have successful treatment

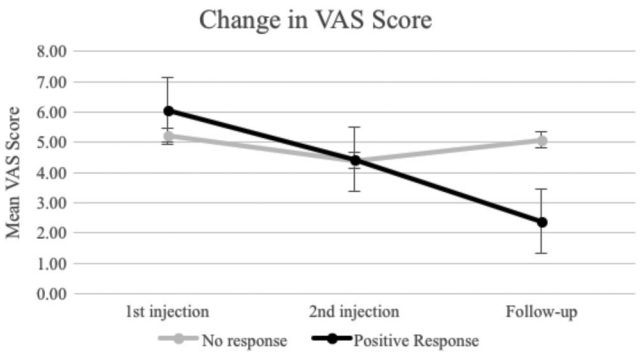

Fig. 2 Mean change in visual analogue score (VAS) from initial injection to follow-up, with 95% confidence intervals (CI), as depicted, for those who did and did not responded positively to treatment

Table 3 Mean Knee Injury and Osteoarthritis Outcome Score (KOOS) and visual analogue scale (VAS) data delineated by response to treatment, with means, standard errors (SE), and *t* test probabilities

	Positive response ($N = 58$)	No response ($N = 44$)	*P* value
VAS score			
Initial	6.1 (2.3)	5.2 (2.3)	0.066
2nd visit	4.4 (2.4)	4.4 (2.3)	0.924
Follow-up	2.4 (2.1)	5.1 (2.7)	**0.001**
Change in VAS	3.7 (2.0)	0.1 (2.0)	**0.001**
Initial KOOS			
Pain	45 (14)	50 (16)	0.075
Symptoms	44 (15)	51 (17)	0.022
ADL	50 (17)	57 (20)	0.067
Recreational	24 (19)	26 (22)	0.621
QoL	28 (16)	31 (18)	0.453
2nd KOOS			
Pain	54 (15)	54 (17)	0.904
Symptoms	55 (15)	55 (18)	0.924
ADL	58 (17)	60 (18)	0.743
Recreational	28 (24)	30 (24)	0.665
QoL	34 (14)	35 (17)	0.733
Follow-up KOOS			
Pain	74 (15)	46 (20)	**0.001**
Symptoms	71 (15)	46 (20)	**0.001**
ADL	75 (15)	51 (22)	**0.001**
Recreational	46 (30)	23 (23)	**0.001**
QoL	52 (18)	29 (20)	**0.001**
Change in KOOS (%)			
Pain	82 (80)	−6 (40)	**0.001**
Symptoms	59 (70)	−42 (120)	**0.001**
ADL	50 (50)	45 (200)	**0.001**
Recreational	64 (180)	−43 (110)	**0.001**
QoL	65 (80)	−36 (140)	**0.001**

A Bonferroni correction was applied to these multiple tests, which rendered a significant *p* value of $p \leq 0.002$; changes in VAS and KOOS from initial visit to follow-up are also depicted

ADL activities of daily living, *QoL* quality of life

with intra-articular injections than those with more advanced OA. This finding was recently corroborated by a retrospective review of the Euflexxa clinical trial database [32]. Patients with higher-grade OA may have insufficient healthy cartilage left to respond to the injection and likely have a higher volume of inflammatory factors, which may minimise HA's effect [9, 10]. Patients who did not respond had a significantly higher rate of arthroplasty at an average of ten months postinjection than those who responded during the follow-up period. While further research is needed to draw definitive conclusions, recent studies indicate that a series of HA injections may delay TKA [33–35].

Age ≥60 years was a significant positive predictor for those with grade 2 OA. This may be explained by a combination of lower physical demand among older patients and higher expectations in younger patients. Previous studies confirm that patients >60 years can have significant improvement with

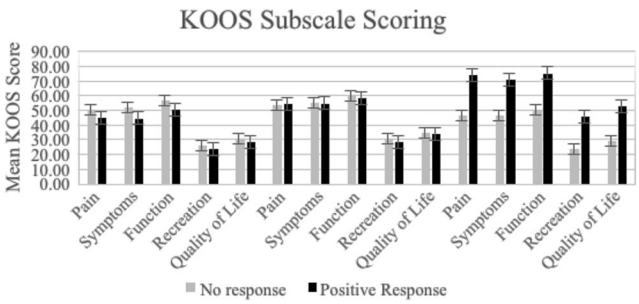

Fig. 3 Analysis of Knee Injury and Osteoarthritis Outcome Score (KOOS) by subgroups, with 95% confidence intervals (CI), as depicted, for those who did and did not responded positively to treatment

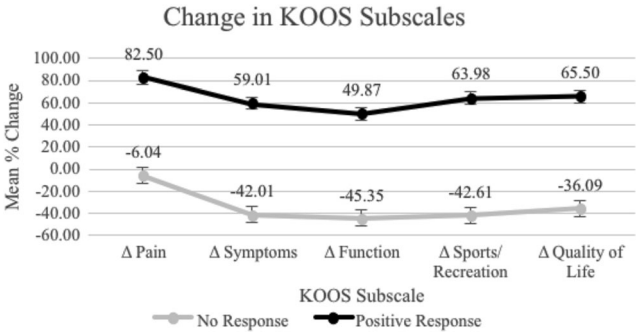

Fig. 4 Mean percent change in Knee Injury and Osteoarthritis Outcome Score (KOOS) subgroups from baseline to follow-up, with 95% confidence intervals (CI), as depicted, for those who did and did not respond positively to treatment

HA injections, but those with advanced OA are less likely to respond [21, 24, 36, 37]. Factors in this study that did not significantly impact success included race, sex, BMI, smoking status, brand of HA and initial KOOS and VAS scores.

Perhaps the most important variable unaccounted for in this and other studies is patient expectations and the placebo effect, which vary greatly and may affect perceived response to treatment [38]. Multiple meta-analyses have found that "placebo," specifically intra-articular saline injection, was an effective treatment for OA [39, 40]. One theory is that a saline injection alone may dilute the inflammatory mediators present in the joint [40]. This may explain why some patients in our study had a positive response even after the first injection. Interestingly, those who did respond to the first injection were twice as likely to have a positive response to treatment at follow-up. Maximal benefit was not observed until the three month follow-up, with gradual improvement throughout the treatment period. This upwards trajectory has been confirmed by previous meta-analyses [41].

From a safety perspective, HA injections have few serious adverse reactions, with the most common being pain and local injection-site reactions [42]. Two patients in this study withdrew because of pain, but there were no major adverse events. A systematic review by Miller and Block found no difference in adverse clinical reactions in HA compared with placebo [43]. Two studies proposed that HA treatments have fewer safety-related events and a better side-effect profile than NSAIDs orally [44, 45].

Strengths of this study are its prospective nature, strict inclusion and exclusion criteria, validated outcome measures and objective analysis. There are several important limitations of this study. Firstly, a small number of patients in certain subgroups could precipitate a type 2 error. Secondly, better patient retention and NSAID diary records would have provided more robust data for analysis and eliminated a potential source of bias. By offering patients a stipend, we attempted to mitigate this problem, though we acknowledge this could introduce a source of bias. Also, this study did not directly evaluate the duration of treatment response. Finally, OA symptoms may unpredictably wax and wane, which further complicates evaluation of treatments for knee OA.

It is important for the physician and patient to define reasonable goals at the outset of treatment. While the role of HA injections in the treatment of knee OA continues to be defined, our study indicates that certain patients are more likely to have a positive response to treatment. This study provides valuable prognostic data for clinicians when counseling patients and recommending treatment:

(1) Patients with mild-to-moderate OA may experience mild-to-moderate relief.
(2) Patients with moderate OA are more likely to respond positively if they are ≥60 years.
(3) A positive response to the first injection is an encouraging predictor for overall treatment success, though patients can expect a progressive improvement in symptoms with subsequent injections.
(4) Patients who respond positively are less likely to undergo knee arthroplasty in the short term.
(5) The VAS appears to be a reliable tool for monitoring and defining treatment success.

Symptom management is the mainstay of non-operative OA treatment. We anticipate further discussion in the literature regarding clinically significant responses, relevance of the placebo effect and ultimate goals of HA treatment. It is important for clinicians to apply this knowledge when forming efficacious and cost-effective treatment plans to achieve the best outcome for our patients.

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Compliance with ethical standards

Conflict of interest Authors Bowman and Hallock declare that they have no conflict of interest. Author Azar has received consultant fees from 98point6, Iovera, and Zimmer and publishing royalties from Elsevier; he serves on the governing/editorial board/committee of the ABOS, Am J Sports Med, Orthop Clin N Am, and St. Jude Children's Research Hospital. Author Throckmorton has received consultant and speaker fees, IP royalties, and research support from Biomet and Zimmer; he receives publishing royalties from Elsevier, and serves on the governing/editorial board/committee of the AAOS, Am J Orthop, American Shoulder & Elbow Surgeons, J Orthop Trauma, Mid-America Orthop Assoc, Orthop Clin No Am, and Tech in Shoulder & Elbow Surgery.

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