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A Six-Month Study on the Efficacy and Safety of a Single Intra-Articular Injection of Sodium Hyaluronate in Knee Osteoarthritis

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Keywords

Viscosupplementation
Hyaluronic Acid
Knee Osteoarthritis
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Abstract

Objective: This single-center, open-label, phase IV study aimed to evaluate the six-month efficacy and safety of a single intra-articular injection of 2% sodium hyaluronate (Hyarelief®) in patients with grade III knee osteoarthritis (OA).

Material and Methods:: Ninety patients aged ≥ 40 years with ACR-defined grade III knee OA received a single injection. Primary outcomes were pain intensity (10-cm Visual Analogue Scale, VAS) and joint function (WOMAC index), assessed at baseline and on days 15, 30, 60, 90, 120, 150, and 180. A linear mixed model with Bonferroni correction analyzed changes over time. Subgroup analyses (Mann-Whitney U test) examined differences by gender, adverse events, and rescue medication use.

Results: A significant effect of time was found for both VAS ($F=263.319$, $p<0.001$) and WOMAC scores ($F=1054.539$, $p<0.001$). Mean VAS decreased from 6.33 ± 1.01 cm at baseline to 1.06 ± 0.90 cm at day 90 ($p<0.001$). Mean WOMAC improved from 0.733 ± 0.099 to 0.309 ± 0.066 at day 120 ($p<0.001$). All follow-up scores were significantly better than baseline (all $p<0.001$). Subgroup analysis revealed significantly higher average pain in males versus females ($p=0.001$) and in patients requiring rescue medication ($p<0.001$). Adverse events were rare (5.6%) and mild.

Conclusion: A single injection of 2% sodium hyaluronate provides statistically and clinically significant improvement in pain and function for up to six months in patients with grade III knee OA, with a favorable safety profile. The treatment effect appears robust, though pain reporting may vary by gender.

Introduction

Knee osteoarthritis (OA) is a common type of degenerative joint illness that is mostly characterized by progressive deterioration of the cartilage, subchondral bone remodeling, synovial inflammation, and clinical symptoms of pain, stiffness, and loss of motion of the patient.¹ This condition is the main cause of disability among the elderly population, resulting in marked social and economic burdens.² Though the symptomatic knee OA management is the most considerable clinical challenge, the main therapeutic goals are still pain relief, joint function upgrade, and the promotion of the quality of life of the patients, particularly the people with advanced illness who are not in the immediate need for surgical intervention.

Oral analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) as the first lines of therapy are on the list of the current pharmacological strategies. The use of the intra-articular (IA) therapies like corticosteroid and hyaluronic acid (HA) injections is another choice.³ HA or viscosupplementation is a treatment

approach designed to coincide with the hypothesis of the pathogenesis of OA which suggests a loss of the concentration and molecular weight of endogenous synovial fluid hyaluronan, and also a consequent decrease in its viscoelastic and protective properties.^{4,15} An alien voice can be given to HA by exogenous administration displaying an aim to bring back the rheological balance, the latter to give it a push with lubrication of the synovial fluid, shock-absorption capability, and a potential initiation of endogenous HA synthesis along with inflammation control and cartilage-like properties.^{5,9}

The efficacy clinical trials of a number of different HA formulas for the treatment of knee OA examined in millions of cases; however, the results were not the same.^{6,7} At the same time, the reviews and the analyses conducted by different teams did not agree, so it would be impossible to say that all the available data concur on a particular point, due to the fact that the total amount of the data do not mentally approve of the idea if they do not like it.^{8,13} It is expected that the patient's reaction to the treatment may show different patterns, based on the molecular weight of the drug, the number of injections, and whether the patient is a severe or a light case.^{11,14} There are also the so-called high molecular weight formulations, such as the one with a single injection of hylan G-F 20, whose main goal is to allow the drug to remain longer in the joint and, in this way, to provide the best clinical results.^{3,7}

Notwithstanding the large number of studies on single-injection protocols, the question of their ability to provide good therapy in the long run is the subject of intense debate. This is a very practical approach because it allows for the patient to be more engaged in the whole process and therefore, the doctor would find no difficulty, while there will be no risk from any injection as a whole.^{10,18} It is also pertinent to mention the studies that have been conducted on the effects of hyaluronic acid injections. These studies have demonstrated outcomes that deviate from the anticipated results, with some cases exhibiting a duration of half a year.^{19,20} Moreover, as supported by non-experimental observational data from the defined cohort of participants with strictly defined characteristics, such as patients of III OA grade, may still give the role of the current therapy in the severe subgroup to the question of the disease maturely confirmed.

Thus, this was an open-label, single-arm, phase IV single-center study and aimed primarily to determine whether the long-term efficacy (six months) of this treatment modality could perfectly fit the treatment needs of patients with knee osteoarthritis. All the patients who were in the grade 3 osteoarthritis were treated by a single intra-articular injection (with Hyarelief) to the knee joint of 2% sodium hyaluronate. The study, through the reliable and

validated tools such as the Visual Analogue Scale (VAS) for estimating the level of pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as a measure of detecting the degree of functioning of the affected body parts, aimed at helping the investigators with the observation of the recovery trend in the patients' symptoms and the recuperation of the functions following a single administration of viscosupplementation in the advanced osteoarthritis.

Materials and Methods

Study Design and Ethical Considerations

The current research was carried out at a single center as an open-label, non-comparative, phase IV clinical study. The study's principal aim was to observe the long-term functionality and safety of a single intra-articular injection of sodium hyaluronate in grade III knee osteoarthritis patients over a period of six months.

Study Population and Eligibility Criteria

Patients who were 40-85 years old and had symptoms having lasted for over three months were eligible, while patients who had undergone consecutive outpatient screening for knee pain were included. The patients were diagnosed with knee osteoarthritis on the basis of the American College of Rheumatology (ACR) criteria, which combine radiographic findings with clinical symptoms and physical signs.¹ The severity level of OA as well as its categorization were conducted using Kellgren and Lawrence grading system, in which patients who were graduated in terms of OA with Grade III were included in the study.²³

An exclusion part of the methodology was defined in such a way that it made sure to take away any changes that could enter the homogeneity of study participants as well as to decrease the impact that may result from deceptive variables. Exclusion criteria involved a variety of systemic diseases like diabetes mellitus, immunodeficiency, vascular disease, history of cancer, autoimmune disorders, or disorders of coagulation such as thrombocytopenia. Patients were also excluded raised local issues if active infection or a wound at the knee site was occasioned, a history of severe knee trauma was recorded, or a malalignment above 20 degrees of genu valgum or varum. Moreover, the other pharmacological exclusions were taking into consideration like NSAIDs intake within two days to further control local factors, a rule was applied, that is, patients had to meet the following points to be included in the study: no hemoglobin <12 mg/dl, no platelet count <150,000/ μ l, no pregnancy, no lactation, no history of vasovagal shock, no hypersensitivity to hyaluronate or avian proteins (egg, chicken, feathers), no concurrent treatment with ACE inhibitors, and no glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Intervention and Follow-up Schedule

All participating individuals were administered the single intra-articular injection of the Hyarelief® sodium hyaluronate at a concentration of 2% on the visit of the day that one of the patients got enrolled in the study (Day 0). Under standard clinical protocol, the injection was delivered after the knee was observed to be infection-free. After confirmation of the absence of local infection or skin lesions, the intra-articular injection was administered under standard aseptic conditions.

Outcome Measures and Assessments

The main excoognitive end points were the change in the pain intensity of the knee and joint function. The instance of the pain form was shown by the slopes on the Visual Analogue Scale of length 10 that ranged from 0 (representing the state with no pain in the field) to 10 (representing the state with the maximum pain). The functional ability of the knee and associated joints was measured by the Likert version of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale (version 3.1), where there are subscores for the three components of the instrument (pain, stiffness, and function).⁸

The patient's individual data, namely serial VAS, WOMAC scores (pain and physical function, WOMAC scores were normalized to a 0–1 scale for analytical consistency.), demographic information (age, gender), osteoarthritis grade, and the detection of post-injection adverse effects, were collected at each visit. The secondary objectives included the overall assessment of the efficacy and tolerability of the treatment, as decided not only by the treating doctor but also by the patient. In particular, patients were also given rescue analgesia with paracetamol or ibuprofen, such painkillers were permitted for ethical reasons. It was mandatory to complete a patient diary to record the use of rescue medications as well as all additional clinical data beyond that obtained during visits, this was done to collect information that was just an indirect indication of the level of pain.

VAS and WOMAC pain and physical function subscores were recorded individually for each patient at every visit. Rescue medication use and its timing were prospectively documented on a per-patient basis.

Ethical Principles

The study took place at the Department of Orthopaedics and Traumatology of Tekirdağ Namık Kemal University after the study protocol had been reviewed and approved by the Clinical Research Ethics Committee (Date:26.03.2024 Decision No: 2024.53.03.17) The patients signed a written consent form and were fully aware of the purpose, method, and voluntary nature of their participation according to the guidelines of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows. After necessary calculations were performed, the researchers computed the descriptive statistics reports for each demographic and clinical variable that existed in the database. The longitudinality of the major outcome scores (VAS and WOMAC) throughout the eight visits was verified by a repeated-measures analysis of variance (Linear Mixed Model). A linear mixed-effects model with subject-specific random intercepts was applied to account for within-patient correlations. According to Bonferroni adjustments, pairwise comparisons were performed between all visits including the baseline and each subsequent visit. For the whole study, a two-sided confidence interval of 95% and a statistical power of 90% were set in advance of analysis.

Results

A total of 90 patients with grade III knee osteoarthritis were enrolled and completed the six-month follow-up period. The demographic and baseline clinical characteristics of the study population are presented in Table 1.

The mean age of the participants was 65.7 ± 9.0 years, with a nearly equal gender distribution (48.9% male, 51.1% female). All patients had radiologically confirmed Kellgren-Lawrence grade III osteoarthritis.

The linear mixed model analysis revealed a statistically significant effect of time on both primary outcome measures. For pain intensity assessed by the VAS, the effect of time was highly significant ($F(7, 521.304) = 263.319, p < 0.001$). This finding was robustly confirmed by the non-parametric Friedman test ($\chi^2(7) = 405.305, p < 0.001$). Similarly, for functional status assessed by the WOMAC index, a profound effect of time was observed in both the linear mixed model ($F(7, 582.502) = 1054.539, p < 0.001$) and the Friedman test ($\chi^2(7) = 467.621, p < 0.001$). A marked and rapid reduction in pain was evident following the intra-articular injection. The mean VAS score decreased from 6.33 ± 1.01 cm at baseline to 3.66 ± 0.96 cm at Day 15,

Table 1: Demographic and Clinical Baseline Characteristic of the patients (n=90)

Characteristic	Value (n=90)
Age (years)	
Mean \pm SD	65.7 \pm 9.0
Range	40 - 83
Gender, n (%)	
Male	44 (48.9%)
Female	46 (51.1%)
Kellgren-Lawrence Grade, n (%)	
Grade III	90 (100%)
Rescue Medication Use, n (%)	13 (14.4%)
Adverse Events, n (%)	5 (5.6%)

demonstrating a significant improvement within the first two weeks ($p < 0.001$). This positive trajectory continued, with the mean score reaching its nadir of 1.06 ± 0.90 cm at the 90-day visit. Although a slight increase was noted at subsequent visits (120, 150, and 180 days), the pain scores at all post-injection time points remained statistically and significantly lower than the baseline value (all $p < 0.001$). A parallel and significant improvement was recorded in joint function. The mean WOMAC score showed a substantial decline from 0.733 ± 0.099 at baseline to 0.404 ± 0.068 by Day 15 ($p < 0.001$). Functional improvement was sustained throughout the study period, with the lowest mean score observed at Day 120 (0.309 ± 0.066). The WOMAC scores at every follow-up visit were significantly better than the pre-treatment scores (all $p < 0.001$) (Figure 1).

Analyses of the six-month average scores for VAS and WOMAC revealed significant associations with specific patient factors, as summarized in Table 2. Male patients reported a significantly higher average pain level over the entire study period compared to female patients (2.60 ± 0.64 vs. 2.19 ± 0.65 , $p = 0.001$). A similar, though less pronounced, gender difference was observed in average WOMAC scores (0.410 ± 0.067 vs. 0.376 ± 0.060 , $p = 0.019$). As expected, and serving as a validation of the pain scale, patients who required rescue analgesic medication had a significantly higher average VAS score compared to those who did not (3.38 ± 0.45 vs. 2.22 ± 0.55 , $p < 0.001$). No significant difference in average WOMAC scores was found between these groups ($p = 0.425$). The occurrence of an adverse event was not associated with statistically different average VAS or WOMAC scores ($p = 0.225$ and $p = 0.515$, respectively) (Table 2).

The single intra-articular injection of 2% sodium

hyaluronate was well-tolerated. Adverse events were reported in only 5 patients (5.6%), all of which were mild and transient, comprising mild injection-site pain or local inflammation. Rescue medication was utilized by 13 patients (14.4%), primarily during the later phases of the follow-up (from the 6th to the 8th visit), which aligns with the observed mild increase in mean pain scores towards the end of the observation period.

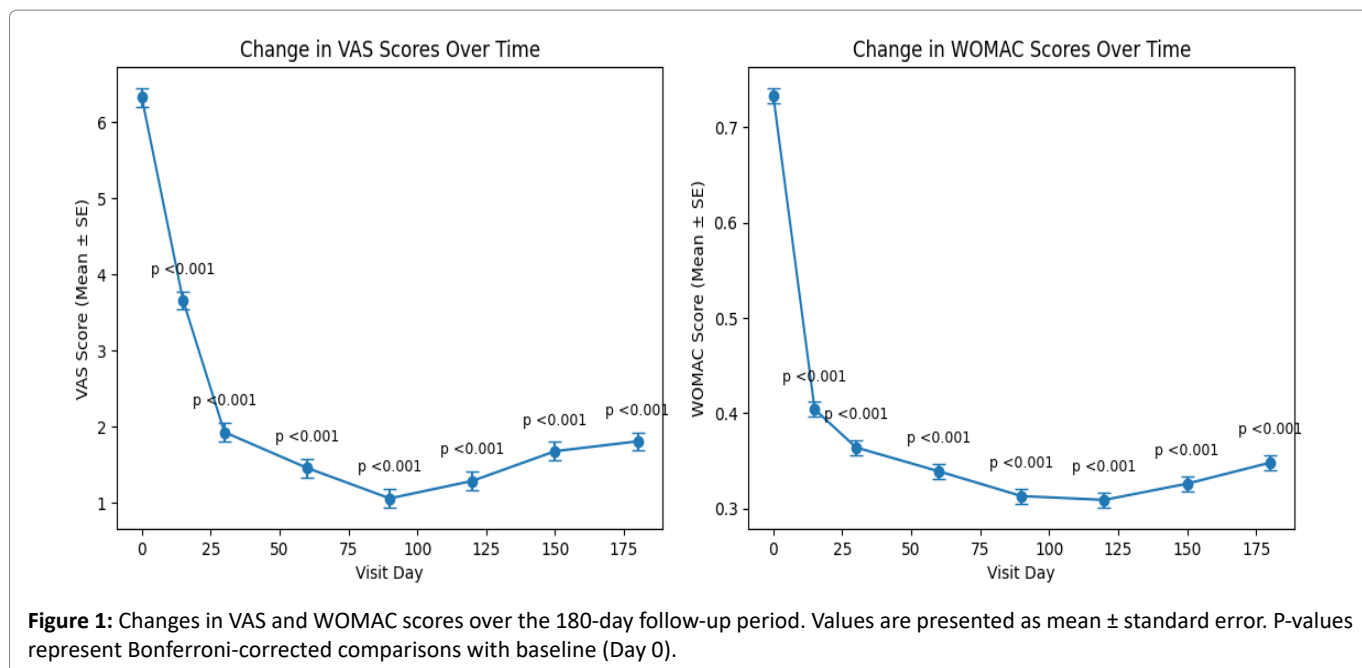
Discussion

Therapeutic interventions to handle moderate to severe knee osteoarthritis (OA) are quite challenging and demand a solution that can relieve the symptoms and not need surgical treatment for a while. Viscosupplementation through hyaluronic acid (HA) intra-articular boost is a new valid and frontline solution that relies on the principle of

Table 2: Six-Month Average Clinical Scores by Subgroups and Comparisons

Subgroup	n	VAS Score, Mean \pm SD	p-value†	WOMAC Score, Mean \pm SD	p-value†
Overall	90	2.39 \pm 0.67	--	0.393 \pm 0.065	--
Gender					
Male	44	2.60 \pm 0.64	0.001	0.410 \pm 0.067	0.019
Female	46	2.19 \pm 0.65		0.376 \pm 0.060	
Adverse Event					
Yes	5	2.73 \pm 0.65	0.225	0.413 \pm 0.072	0.515
No	85	2.37 \pm 0.67		0.392 \pm 0.065	
Rescue Medication Use					
Yes	13	3.38 \pm 0.45	<0.001	0.406 \pm 0.066	0.425
No	77	2.22 \pm 0.55		0.391 \pm 0.066	

p-value: From Mann-Whitney U test for comparisons between subgroups



regenerating the viscoelastic properties of pathological synovial fluid.¹⁵ The current open-label study adds to the existing evidence to the growing body of evidence and hence new data with one single injection of 2% sodium hyaluronate (Hyarelief®) show statistically significant and clinically meaningful decreases in pain and functional disturbances for six months in grade III knee OA patients. These findings are supported by biologically directed HA therapy and confirmed by a number of the most relevant studies in the literature which, in addition, provide the emergence of patient response patterns.

A substantial reduction (with a mean VAS score drop of approximately 4.3 cm on Day 30) of pain, was registered. A reasonable early impact of such magnitude in pain relief raises the fact that there are studies of the same kind of treatment which also support this initial statement. For example, Altman et al., say that a single injection of non-animal stabilized HA (NASHA) resulted in significant pain reduction from week 1 through week 26.⁸ Besides, Chevalier et al. performed a large scale placebo-controlled trial and confirmed that hylan G-F 20 delivered pain and function benefits from one shot than placebo throughout 26 weeks.⁷ Our finding of the greatest effect at the 90-day visit remains in keeping with tradition where already mentioned peak benefit is commonly observed within the first 8 to 12 weeks following an injection and gradual attenuation to the sixth month. The subsequent mild, although statistically significant, increase in pain scores at the 150- and 180-day visits illustrate a weakening of immediate pain relief, a situation corresponding to the HA's characteristics of being time-segmented in the admitted site and thus, as an indication the therapy acts as a mid-term symptomatic option.²¹

The corresponding, meaningful improvements in the physical function component of the WOMAC index further validate the broader effect of pain relief on joint mechanics and patient activity. The gains in functionality seen in this trial are as per the balances and the functioning tests completed by Sun et al., who demonstrated significant improvements in geriatric patients' balance and physical function following HA injection over a period of six months.⁴ These sustained gains in function in conjunction with the slight rebound after pain scores may indicate that the return of mobility and confidence to the joint has a more extended influence, or that HA performs rather slowly in disease modifying operations suggesting chondro-protection or anti-inflammatory functions beyond analgesia as surmised in catalytic references.^{16,17} However, the strong correlation expected between pain relief and function improvement underscores that the primary mechanism of action likely remains symptomatic relief.¹

Among the very noticeable findings of our subgroup analysis was the very strong connection of male gender

to higher level of average pain scores throughout the whole study. In other words, males were more frequent in the higher average pain score category so they had more pain. The latter is a possible indicator of either a different experience or an explanation of gender-related pain-related trigger factors or else a stronger link to a specific disease phenotype or its severity. It becomes a must then to look deeper into the issue. Highlighting of the gender aspect vis-a-vis the pain score is relatively uncommon in major HA efficacy trials, but demographic aspects like sex are nonetheless important in the context of personalized medical treatment. On the other hand, the absence of a significant relationship between negative events and the clinical results is a benefit and it is certainly in harmony with documented data truth, because most of the minor and the transient local reactions in the case of HAS have been the ones depicted.^{6,12,13} The fact that patients using rescue medication reported substantially higher average pain scores is a strong internal validation of the VAS scale and highlights the clinical importance of the pain levels recorded. This can be seen as a method of triangulating the subjective report with objective behavior (analgesic use).

On the basis of a wider evidence base, our results help to justify the single-injection protocols' efficacy. Some earlier trials, for example, the Lundsgaard et al. study, have demonstrated that saline injections can produce considerable placebo effects. However, the scale and duration of improvement in our patients, particularly in a strictly defined grade III OA population, appear to exceed what is typically reported for placebo responses.⁵ Besides that, the findings advocate for the continued use of HA in patients with advanced radiographic disease, a group sometimes considered to have a lower response rate. This is in line with Conrozier et al.'s findings for the hip, which, while identifying factors that predict response, also showed that the treatment is effective in severe OA.²⁰

The results of this study should nevertheless be seen only in the light of its methodology. The open-label, single-arm design, although it mirrors everyday clinical practice, does not allow for firm conclusions about the superiority of the treatment over placebo or other active treatments such as intra-articular corticosteroids or oral therapies like diacerein.² Without a control group, the changes seen in the patients combine the specific treatment effect and the non-specific contextual effects that are present in any kind of therapeutic intervention.¹⁸ Also, the six-month follow-up period, which is quite common in many HA studies, does not provide information on the long-term course or the possible need for and best time for repeat injections.^{9,14}

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of the treatment over placebo or other active treatments such as intra-articular corticosteroids or oral therapies like diacerein.² Without a control group, the changes seen in the patients combine the specific treatment effect and the non-specific contextual effects that are present in any kind of therapeutic intervention.¹⁸ Furthermore, this study evaluated a specific preparation of non-crosslinked, medium molecular weight, 2% sodium hyaluronate. While the results are positive, direct comparative efficacy conclusions against other single-injection HA formulations cannot be drawn from this single-arm study. The rigorous patient selection, strictly limited to symptomatic Kellgren-Lawrence grade III OA, might have contributed to the observed consistent treatment effect by minimizing heterogeneity. Future head-to-head comparative studies are needed to elucidate whether specific product characteristics or the selection of a homogeneous patient population with advanced radiographic disease is the primary driver of the favorable outcomes reported here. Also, the six-month follow-up period, which is quite common in many HA studies, does not provide information on the long-term course or the possible need for and best time for repeat injections.^{9,14}

In conclusion, this study provides pragmatic evidence that a single intra-articular injection of 2% sodium hyaluronate is an effective and well-tolerated treatment option for alleviating pain and improving function in patients suffering from grade III knee osteoarthritis for up to six months. The significant gender-based difference in pain reporting highlights an area for further research into personalized treatment approaches. Future investigations should aim to corroborate these findings in randomized, controlled settings with longer follow-up durations and to explore biomarkers or clinical predictors that can reliably identify the patients most likely to derive substantial and durable benefit from this minimally invasive intervention.^{19,22}

Declarations

Acknowledgment

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Conflicts of Interest

None of the authors have any conflicts of interest.

Funding

No sponsors were involved in this study.

Data Availability

Data available on request from the authors.

Consent to Participate

All participants signed the Free and Informed Consent Form before the start of the study.

Consent for Publication

Authors provide consent for publication of article.

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