



Effectiveness of gonarthrosis treatment via intra-articular injections of linear vs. cross-linked hyaluronic acids

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Knee osteoarthritis (OA) is a condition characterized by significant pain resulting from the gradual deterioration of joint cartilage.^[1,2] The incidence of OA has been rapidly increasing due to the aging population. Managing OA presents a formidable therapeutic challenge due to its intricate pathophysiology and limited effective treatments. Despite the array of therapeutic options available, the current lineup primarily focuses on alleviating clinical symptoms rather than addressing the underlying disease causes.^[2,3]

For mild cases of OA, approaches such as patient education, pain management, and lifestyle adjustments are commonly employed. These include incorporating physical therapy and rehabilitation techniques. A broad spectrum of pharmacological treatments is available for OA patients. These

ABSTRACT

Objectives: The study aimed to compare the outcomes of single-dose cross-linked hyaluronic acid and the linear regimen of three doses of HA knee injections among patients with gonarthrosis.

Patients and methods: This single-center, retrospective study was conducted with 60 patients (47 females, 13 males; mean age: 57.9±4.29 years; range, 50 to 65 years) with Kellgren-Lawrence Grade 2 or 3 gonarthrosis between February 2020 and February 2022. Patients were either subjected to intra-articular cross-linked hyaluronic acid (n=30) or linear hyaluronic acid (n=30) injection treatments. Comprehensive assessments of the patients were conducted prior to the injections, as well as at three and six months after injection. The two injection groups were compared regarding the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Oxford Knee Score.

Results: Both injections showed a statistically significant improvement from baseline in both WOMAC and Oxford Knee Score at three and six months (p<0.001). There was no notable distinction in the alteration of WOMAC knee scores between the two injection types. However, a notable discrepancy was observed in the elevation of Oxford Knee Score among patients who received cross-linked knee injections compared to those who underwent linear hyaluronic acid knee injections, signifying a significant increase in the former group (p<0.001).

Conclusion: The advantage of a single-dose administration of cross-linked HA knee injections, as opposed to the three-dose regimen required for linear hyaluronic acid, translates into reduced time and cost for the injection process. Moreover, this approach minimizes injection-associated discomfort for patients due to the singular dose administration.

Keywords: Conservative treatment, gonarthrosis, hyaluronic acid, viscosupplementation.

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encompass symptomatic slow-acting medications, topical treatments, nonsteroidal anti-inflammatory drugs, steroids, and even opioids in appropriate cases. The necessity for joint replacement surgery depends on the severity of the condition.^[4,5]

While intra-articular injection therapies form a cornerstone of nonsurgical approaches for OA patients, there exists controversy regarding the optimal injectable treatment for such individuals.^[2] Hyaluronic acid (HA) injections present an alternative option for treating OA by replenishing synovial fluid and restoring joint viscoelasticity.^[6,7] Several studies have demonstrated the benefits of HA for OA patients,^[6,8] and this widely distributed glycosaminoglycan is naturally found in human cartilage, synovial fluid, and membranes.^[9]

Given its critical role in synovial fluid, HA might have the potential to shield soft tissue surfaces and articular cartilage from damage during joint movement when administered through injection.^[10] Consequently, the reparative mechanisms that govern lubrication and the dissipation of mechanical forces within the joint microenvironment are reinstated following intra-articular administration of HA. This administration aims to enhance the viscoelastic fluid.

Intra-articular HA treatment aims to restore the synovial fluid to its original HA properties in the case of OA. Therefore, using HA supplements that resemble healthy synovial fluid is a rational approach.^[11]

Hyaluronic acid cross-linking refers to a process by which HA chains are chemically bound with a chemical cross-linker through one of the HA functional groups (-OH, -COOH, -NHCOCH₃). Cross-linking enhances the stability and viscosity of linear HA, leading to a slower breakdown of HA within the body. Consequently, a single long-acting injection suffices for treatment, as supported by references.^[12-14] In contrast, non-cross-linked HA necessitates multiple injections.^[9] Furthermore, distinctions exist between these HA formulations in terms of various product attributes. These encompass factors like the extent of HA cross-linking, dosing regimen, injection volume, origin, concentration, and molecular weight of the compound. However, there is limited consensus on the significance of these differences.^[9]

The cross-linking technique allows for the creation of a molecular weight-based gel of 5 to 6 million daltons (the average molecular weight of HA in a healthy joint).^[15] This technique increases the molecular weight of HA molecules through covalent cross-links, thereby extending the retention time in the joint after injection. The process of cross-linking in the formulation aims to extend the efficacy duration by heightening resistance to degradation within the joint.^[6]

The objective of this study was to conduct a retrospective analysis of the impacts of intra-articular cross-linked HA treatment compared to linear HA treatment on the knee assessment scores of patients with OA. The study specifically emphasized the outcomes observed at three and six months following the treatment.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the Kütahya Health Sciences University Hospital, Department of Orthopedics and Traumatology between February 2020 and February 2022. The study sample consisted of 60 OA patients (47 females, 13 males; mean age: 57.9±4.3 years; range, 50 to 65 years). Data of the patients were retrieved from the medical records in the hospital database, and no additional interventional procedures were performed. The inclusion criteria were as follows: patients who underwent either type of HA injection (linear or cross-linked HA; the decision of which injection type to apply was left to the patient); age >50 years; knee scores obtained before injection and at three and six months after injection; patients with Kellgren-Lawrence Grade 2 or 3 gonarthrosis; being followed in our center; patients who have been followed for at least six months; patients who had previously received conservative treatment and whose treatment was unsuccessful. The exclusion criteria were as follows: patients with missing data; age <50 years; patients who have received HA treatment in another center; Stage IV gonarthrosis in Kellgren-Lawrence gonarthrosis staging; body mass index >30; knee alignment varus >15° or valgus >15°; patients with active infection, cancer, and peripheral neuropathy.

Patients were randomly divided into two intra-articular knee injection treatment regimen groups with 30 participants in each group: those who underwent intra-articular injections of cross-linked HA (single dose) and those who received intra-articular injections of linear HA (three doses, once a week). A comparison of the functional outcomes was conducted resulting from two distinct injections: a 2 mL dose of 2.4% 48 mg cross-linked HA (SO Visc Cross-Linked; Biolot Medical, Ankara, Türkiye) and a 2 mL dose of 2.4% 48 mg linear HA (SO Visc; Biolot Medical, Ankara, Türkiye) knee injection. The molecular weight distribution of sodium hyaluronate in standard HA injections is 1.6 to 2.4 million daltons. Moreover, it does not contain HA fragments lower than 500,000 daltons. In cross-linked HA injections, the

molecular weight distribution of cross-linked HA is between 5 to 6 million daltons.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)^[16,17] and Oxford Knee Score (OKS)^[18] were calculated in the assessment of knee scores. The WOMAC questionnaire uses a numeric scale from 0 to 4: None=0, Mild=1, Moderate=2, Severe=3, and Extreme=4. A potential score spectrum of 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function is produced by averaging the cumulative results for each subcategory. Although there are other methods for combining scores, the total WOMAC score is typically the sum of the scores obtained from the three different subdimensions. This individual's overall WOMAC score serves as a gauge of their level of pain, stiffness, and functional impairment.^[17]

The OKS was developed to measure pain and function following a total knee replacement.^[18] For knee replacement checks, the OKS is the major outcome metric of preference.^[19] In addition, the OKS was used to evaluate the effectiveness of treatment modalities other than total knee replacement.^[20]

Statistical analysis

Data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Numbers and percentages were used to represent descriptive

data. The Pearson chi-square test and independent samples t-test were utilized to compare groups based on categorical variables. The Kolmogorov-Smirnov test was used to assess the suitability of continuous variables for a normal distribution. Analysis of variance was utilized to compare mean values across various groups. By using correlation analysis, relationships between continuous variables were assessed. The relationship between continuous variables was tested using logistic regression. Mauchly's test was applied for the assumption of sphericity for the application of two-way analysis of variance in repeated measures. Afterward, the Greenhouse-Geisser test results were evaluated in the analysis. The results were evaluated using a 95% confidence interval, and a p-value <0.05 was considered statistically significant.

RESULTS

Demographic data and functional scores of 30 patients from both injection groups who met the inclusion and exclusion criteria and completed their treatment with six-month functional follow-up are shown in Table I.

Age, sex, OA stage, body mass index, and the pretreatment OKS and WOMAC scores did not significantly differ from each other. In this study, swelling and joint pain lasting approximately 24 h were observed in two patients in the group that was

TABLE I
Baseline characteristics and functional scores of patients

| | Standard HA injection (n=30) | | | Cross-linked HA injection (n=30) | | | p |
|---------------------------------------|------------------------------|-----------|-----------|----------------------------------|-----------|---------|--------------|
| | n | Mean±SD | Min-Max | n | Mean±SD | Min-Max | |
| Age (year) | | 57.8±4.2 | 50-65 | | 58.0±4.4 | 50-65 | 0.858 |
| Sex | | | | | | | 0.785 |
| Male | 6 | | | 7 | | | |
| Female | 24 | | | 23 | | | |
| Body mass index (kg/m ²) | | 26.4±1.1 | 25.3-27.5 | | | | 0.317 |
| Localization | | | | | | | 0.785 |
| Right | 16 | | | 15 | | | |
| Left | 14 | | | 15 | | | |
| WOMAC score (0 th month) | | 46.36±7.6 | 30-60 | | 46.06±9.4 | 30-60 | 0.893 |
| WOMAC score (3 rd months) | | 55.30±7.0 | 38-64 | | 53.93±9.0 | 38-67 | 0.368 |
| WOMAC score (6 th months) | | 64.10±6.5 | 46-70 | | 62.96±7.5 | 47-75 | 0.337 |
| Oxford score (0 th month) | | 25.23±3.4 | 20-31 | | 26.60±4.5 | 20-34 | 0.189 |
| Oxford score (3 rd months) | | 34.03±3.4 | 28-40 | | 38.27±4.1 | 28-44 | 0.001 |
| Oxford score (6 th months) | | 40.7±3.3 | 33-46 | | 48.9±4.0 | 42-57 | 0.001 |

HA: Hyaluronic acid; SD: Standard deviation.

treated with cross-linked HA as a minor adverse event. No complaints occurred in the other patients included in the study.

Both injections showed a statistically significant improvement from baseline in both WOMAC and OKS at three and six months. The change in WOMAC knee score did not differ between injection types. The increase in OKS in patients undergoing cross-linked knee injection was compared to linear HA knee injection was significantly higher (Table I).

According to Mauchly's test, the assumption of sphericity was not met since $p < 0.05$. The change in OKS generally differed according to injection types ($F = 26.33$; $p < 0.001$).

The change in OKS generally differed over time ($F = 1256.48$; $p < 0.001$). The change in OKS over time differed according to injection types ($F = 41.39$; $p < 0.001$; Table II). The change in WOMAC did not differ in general according to injection types ($F = 0.22$; $p = 0.64$).

| TABLE II Comparison of OKS between groups | | | | | |
|--|----------------------------------|-------|-------------|----------|----------|
| Source | Tests of within-subjects effects | | | | |
| | Type 3 sum of squares | df | Mean square | F | <i>p</i> |
| Groups | 952.200 | 1 | 952.200 | 26.331 | <0.001 |
| Time | | | | | |
| Sphericity assumed | 10722.478 | 2 | 5361.239 | 1256.484 | <0.001 |
| Greenhouse-Geisser | 10722.478 | 1.778 | 6031.710 | 1256.484 | <0.001 |
| Huynh-Feldt | 10722.478 | 1.862 | 5759.950 | 1256.484 | <0.001 |
| Lower-bound | 10722.478 | 1.000 | 10722.478 | 1256.484 | <0.001 |
| Groups* time | | | | | |
| Sphericity assumed | 353.233 | 2 | 176.617 | 41.393 | <0.001 |
| Greenhouse-Geisser | 353.233 | 1.778 | 198.704 | 41.393 | <0.001 |
| Huynh-Feldt | 353.233 | 1.862 | 189.751 | 41.393 | <0.001 |
| Lower-bound | 353.233 | 1.000 | 353.233 | 41.393 | <0.001 |

OKS: Oxford Knee Score.

| TABLE III Comparison of WOMAC scores between groups | | | | | |
|--|----------------------------------|-------|-------------|---------|----------|
| Source | Tests of within-subjects effects | | | | |
| | Type III sum of squares | df | Mean square | F | <i>p</i> |
| Groups | 39.200 | 1 | 39.200 | 0.222 | 0.639 |
| Time | | | | | |
| Sphericity assumed | 8998.678 | 2 | 4499.339 | 720.999 | <0.001 |
| Greenhouse-Geisser | 8998.678 | 1.595 | 5642.587 | 720.999 | <0.001 |
| Huynh-Feldt | 8998.678 | 1.661 | 5417.763 | 720.999 | <0.001 |
| Lower-bound | 8998.678 | 1.000 | 8998.678 | 720.999 | <0.001 |
| Groups* time | | | | | |
| Sphericity assumed | 9.433 | 2 | 4.717 | 0.756 | 0.472 |
| Greenhouse-Geisser | 9.433 | 1.595 | 5.915 | 0.756 | 0.445 |
| Huynh-Feldt | 9.433 | 1.661 | 5.679 | 0.756 | 0.450 |
| Lower-bound | 9.433 | 1.000 | 9.433 | 0.756 | 0.388 |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

The change in WOMAC generally differed over time ($F=720.99$; $p<0.001$). The change in WOMAC over time did not differ according to injection types ($F=0.75$; $p=0.44$; Table III).

DISCUSSION

The cross-linked HA injection's efficiency in reducing pain and enhancing everyday activities was the study's most important inquiry. Additionally, since it is a single-dosage injection, it takes less time, costs less, and causes less pain to the patient during the injection. This approach was more effective than intra-articular linear HA injection, requiring three injections. Both injections showed a statistically significant improvement from baseline in WOMAC knee scores at three and six months, with no significant difference from each other. In individuals receiving cross-linked knee injection as opposed to linear HA knee injection, the increase in OKS was significantly higher.

Grades II-III of the Kellgren-Lawrence classification were used as the selection criterion in our study. As previously mentioned,^[21] patients with Kellgren-Lawrence IV OA were purposefully left out of this study since intra-articular therapy was shown to be less effective in this particular subgroup.

The main goals of therapeutic interventions for knee OA are to reduce pain and functional impairment. As of right now, no approved treatments have shown definite disease-modifying effects. The standard of care includes pharmacological interventions such as tramadol and nonsteroidal anti-inflammatory drugs, along with lifestyle changes such as physical therapy, exercise routines, and weight loss. Viscosupplementation, which involves injecting HA or corticosteroids into the affected joints, is another recommended treatment option for knee OA.^[22] For the treatment of knee OA, an intra-articular injection is a reported safe and effective minimally invasive technique.^[23] Intra-articular HA and platelet-rich plasma injections are among nonsurgical approaches for treating individuals with knee OA.^[24]

Different intra-articular HA supplementation manufacturing processes lead to variations in product properties, such as the need for a single or series of injections, injection volumes, concentrations, molecular weights, and chemical compositions.^[9,25] Rooster combs were used as a source of HA for the earliest intra-articular products. However, due to the inherent dangers

of using sources derived from animals, these products occasionally resulted in injection site symptoms that resembled pseudoseptic arthritis.^[26-28] Thus, bacterial fermentation is the primary manufacturing method for recently developed HA compounds.^[29] Recently, a novel, nonavian-origin hyaluronate called cross-linked HA was developed. It is useful for treating knee OA. Its initial injection was reported to be efficient and secure for 12 weeks, and injections given repeatedly at 24 weeks are efficient and secure until 36 weeks.^[12,30]

Hyaluronic acid has the ability to cross-link or conjugate with various biomacromolecules, and it can successfully encapsulate a variety of drugs, even at the nanoscale.^[31]

Viscosupplementation is as effective as some nonsteroidal anti-inflammatory drugs, and has longer-lasting effects in some cases, according to two recent systematic reviews.^[6,32] When other nonoperative options fail, intra-articular HA administration appears to be helpful.^[3,30,33]

In the context of treating OA, only the use of high-molecular-weight HA has proven to have a more effective therapeutic effect than nonselective nonsteroidal anti-inflammatory drugs and selective COX (cyclooxygenase)-2 inhibitors. This finding might help explain the contradictory and ambiguous conclusions that are evident in the body of existing literature. Additionally, although high-molecular-weight HA for knee OA offers long-lasting symptom relief,^[34] the American Academy of Orthopaedic Surgeons (AAOS) guidelines only recommend it at a moderate strength.^[14]

Any novel HA derivative is required to be thoroughly evaluated in accordance with clinical safety benchmarks, and its tolerability with regard to tissue responses must also be investigated. This is an important issue that deserves careful thought. There have been reports of HA systems causing significant granulomatous allergic tissue reactions in certain cosmetic applications, despite the fact that high-molecular-weight HA injections used to treat conditions such as bone damage are known to be safe with regard to inflammatory reactions and toxicity.^[35,36] In HA-based release systems, even trace amounts of specific protein contaminants can result in granulomatous tissue reactions.^[37]

In a recent systematic review and meta-analysis, 89 trials involving 12,667 adults were examined in

relation to viscosupplementation for knee OA.^[38] These included 22 cross-linked HA variants, a sham control in 68, a three-month follow-up period in 40, and a sham control in 68. Data from 71 trials involving 9,617 patients were combined, and it was discovered that viscosupplementation had a moderately positive effect on pain. An asymmetric funnel plot revealed relationships between effect size and trial size, blinded outcome assessment, and publication status, as well as evidence of notable trial heterogeneity. Fourteen trials (3,667 patients) revealed an elevated risk of severe adverse events, in contrast to six trials (811 patients) that suggested an elevated risk of flare-ups despite their statistical insignificance. These results highlight the viscosupplementation's numerous benefits for treating knee OA.^[38] Both the linear HA group and the cross-linked HA group in our study of 60 patients did not experience any negative side effects. However, due to the retrospective design, these side effects may have been overlooked.

The study has some limitations. This study was conducted at a single facility with a small group of patients and is retrospective in design. Additionally, the study does not include patient outcomes after the sixth month.

In conclusion, the newly developed, single-injection, cross-linked HA substance exhibits significant potential as a workable therapeutic option for the management of gonarthrosis, according to the conclusions drawn from this investigation. The combination of improved efficacy and a clear safety profile highlights the advantageous nature of this novel intervention, necessitating careful consideration of it for ensuing clinical applications aimed at addressing the complexities related to gonarthrosis. However, it is crucial to substantiate these findings through investigations of a prospective nature, encompassing a larger cohort of patients with long-term results, to validate the outcomes of this study.

Ethics Committee Approval: The study protocol was approved by the Kütahya University of Health Sciences Non-Interventional Clinical Research Ethics Committee (date: August 16, 2023. No: 2023/09-35). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, interpretation, writing the article: S.Y., A.F.K.; Data collection: S.Y., M.K.; Analysis: S.Y., M.K., A.F.K.; Literature review, final approval: S.Y., A.Y. Critical review, materials: A.F.K., S.Y., A.Y.

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