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Original Article

Comparison of Two Different Intraarticular Hyaluronic Acid Injection Regimens in Knee Osteoarthritis: A Randomized Clinical Trial

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ABSTRACT

Objective: The purpose of this randomized clinical trial was to compare the pain and knee function between a single-dose (Sodium hyaluronate 3%, 2 ml, 60 mg) versus two-weekly (Sodium hyaluronate 1.6%, 2 ml, 32 mg) intraarticular hyaluronic acid (HA) injections in mild to moderate symptomatic knee osteoarthritis (OA).

Materials and Methods: Sixty patients with clinically and radiographically confirmed knee OA were randomly divided into two groups for two HA injection regimens. The first group received a single-dose 60 mg HA, while the second group received two-weekly 32 mg HA injections. Pain and knee function were evaluated with the Visual Analogue Scale (VAS) and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) before injection and first, third, and sixth months after injections.

Results: There was no significant difference in baseline characteristics, including age, sex, body mass index, and OA grade, between the two groups (p:n.s. for all variables). Our analysis showed that total WOMAC and VAS mean scores improved compared to the baseline measurements ($p<0.001$ for both scores). However, regarding the minimal important change (MIC) values for both VAS and WOMAC, there was no significant difference between the groups at the final follow-up ($p=0.217$ and $p=0.500$, respectively). An adequate pain reduction could not be achieved in more than half of the patients (56.6%), and almost half (45%) did not have a clinically significant increase in knee function at the final follow-up according to MIC values. No major complications were seen.

Conclusion: This study failed to show a significant benefit or clinically important change after viscosupplementation regardless of the tested dosing regimens.

Keywords: Knee, osteoarthritis, hyaluronic acid, viscosupplementation, WOMAC, Intra-articular injections

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INTRODUCTION

Primary knee osteoarthritis (OA) is a common disease affecting a significant number of subjects older than 50. In a recent meta-analysis on population-based observational studies, the pooled global incidence of knee OA was 203/10,000 person-years (95% CI, 106–331) in subjects older than 20 years [1]. It is characterized by loss of cartilage, derangements of the subchondral bone and synovial tissue, inflammation, osteophyte formation, and degeneration of all structures forming the joint. Patients with knee OA experience pain, loss of knee motion, deformity, and, consequently, loss of quality of life [2]. During the early stages of the disease, conservative treatment is usually chosen. Several methods might be used for symptomatic relief of symptoms, including weight loss, using walking aids, structured land-based exercise programs and physiotherapy, topical or oral anti-inflammatory drugs, oral supplements such as glucosamine, and a variety of intraarticular injections, including hyaluronic acid (HA), platelet-rich plasma (PRP), and corticosteroids [3,4].

HA, a major component of the cartilage extracellular matrix, is produced and secreted by chondrocytes and synoviocytes. Injections of HA, also known as viscosupplementation, have been used as a treatment for knee OA since getting clearance in Japan and Italy in 1987-1988. The idea behind this treatment is to supplement the natural HA in the joint, re-establish the synovial fluid's characteristics, which can become depleted in OA, and improve the lubrication and cushioning of the joint to reduce pain and improve function [5-7]. Currently, several HA products are available on the market with different molecular weights, concentrations, volumes, and a number of injections recommended.

Several previous studies have shown the safety and efficacy of HA injections for knee OA [8-11]. However, controversy still exists on the best injection regimen. A wide range of administrations, at different molecular weights and structures, quantities, and at different injection intervals (a single injection to 5 weekly injections), have been reported up-to-date [12-14]. Some studies have suggested that a single high-dose HA injection may be as effective as multiple lower-dose injections, while others have found that multiple injections provide better results [15-24]. On the other hand, a single high-dose HA injection might reduce patient visits, the number of invasive procedures, and the overall cost. The hypothesis for this study was that a single 60 mg injection of intra-articular HA would be as safe and effective as two weekly 32 mg injections in reducing pain and improving knee function in patients with mild to moderate knee OA. The purpose of this randomized clinical trial was to compare the pain and knee function following either single-dose (Sodium hyaluronate 3%, 2 ml, 60 mg) or two weekly (Sodium hyaluronate 1.6%, 2 ml, 32 mg) intraarticular HA injections.

MATERIALS AND METHODS

Patients and Study Design

This study was a prospective randomized controlled clinical trial (RCT) that included patients with mild to moderate knee OA who were elected for intra-articular HA injection. The study was conducted in a tertiary university hospital between 2020 and 2021. Patients who received any previous intraarticular injection, who underwent previous knee surgery, who have a history of inflammatory diseases such as rheumatoid arthritis, posttraumatic knee OA, neuromuscular disorders, history of psychiatric illness, body mass index (BMI) greater than 40 kg/m^2, and patients who denied participation were excluded from the study. Knee OA criteria set by the American College of Rheumatology were used for the diagnosis [24]. Patients with mild to moderate knee OA (grade II and III), according to Kellgren–Lawrence radiographic grading scale, were assessed for eligibility.

The study was conducted according to the ethical standards in the 1964 Declaration of Helsinki and its later amendments, and the institutional review board approved the study protocol (IRB approval date/issue: 07.11.2019, 24/2). Informed consent was obtained from the participants. The study followed the guidelines for RCTs outlined in the "CONSORT statement." [25].

Sample Size Calculation and Randomization

The sample size was computed using the G*Power program (Ver. 3.1.9.6, Dusseldorf, Germany). The power of the study was predicted to be 90% when 28 patients in each group (total: 56 with equal allocation ratio) were included at the level of two-tailed alpha (0.05) and effect size 0.99 based on the study by Zoboli et al. [16]. Considering the possibility of drop-out from the study after enrollment, 60 patients were included. The opaque sealed envelope method was used to achieve allocation concealment for randomization. Sixty envelopes were prepared and mixed. On the day of the HA injection, one envelope was chosen and removed from the pool. Both the physician and the patient were not blinded to the intervention.

The content of the Injections

Two different doses of HA were used for this study. HA injection was provided in a sterile 2 ml glass syringe. In the single injection group, (Sodium hyaluronate 3%, 2 ml, 60 mg) was used. In the two-weekly injection group, (Sodium hyaluronate 1.6%, 2 ml, 32 mg) was used. The product was a biologically fermented HA with a molecular weight of 2.9-3.8 mDa for 32 mg injections and 1.8-2.5 mDa for 60 mg injections. Table 1 summarizes the content of the HA preparations.

Table 1. The content of the HA injections used in the study

Composition	Single injection	Two-weekly injections
Volume	2.0 ml	2.0 ml
Sodium Hyaluronate	60 mg	32 mg
Sodium Chloride	17 mg	17 mg
Disodium Hydrogen Phosphate	1.126 mg	1.126 mg
Sodium Dihydrogen Phosphate	0.090 mg	0.090 mg
Molecular weight	1.8-2.5 mDa	2.9-3.8 mDa
Osmolality	270 - 400 mOsm/kg	270 - 400 mOsm/kg
pH	6.8 - 7.6	6.8 - 7.6
Zero Shear Viscosity	350.000 - 650.000 mPa.s	350.000 - 550.000 mPa.s
Water for injection	q.s	q.s

q.s. : quantum sufficit; mDa: million Dalton.

Radiological Evaluation

All patients had standing posteroanterior (PA) and lateral knee radiographs with the X-ray beam centered on the knee joint line. Kellgren–Lawrence radiographic grading scale was used to classify the radiological grade of knee OA [26]. Radiological ratings were performed on digital radiographs stored in picture archiving and communication systems (PACS) by two independent observers once using the software program Sectra IDS7 (Ver. 18.2., Sectra AB, Linköping, Sweden) on the digital workstation. K-statistics were used to establish a relative level of agreement between the observers. The agreement was graded as slight (κ=0–0.2), fair (κ=0.21–0.40), moderate (κ=0.41–0.60), substantial (κ=0.61–0.80), and almost perfect (κ=0.81–1) according to Landis and Koch [27]. Interobserver reliability was found to be substantial (κ=0.645). There were three patients on whom agreement could not be reached. The two observers mutually decided on these patients for the final analysis.

Injection Technique

The superolateral approach was chosen for the intraarticular knee injection. The patients were placed in the supine position with the knee in extension. After sterile knee preparation, the superolateral border of the patella was palpated, and the patella was gently tilted medially to ease access to the joint. A 21 G needle with a 10 mL syringe was inserted underneath the patella to gain access to the joint space. Synovial fluid was aspirated, if present, as much as possible; the needle was left inside the joint without changing the position, and the syringe was replaced with HA containing syringe. The injection was completed within ~10 seconds, and the needle puncture was closed with a sterile adhesive strap.

Follow-up and Data Collection

The pain was assessed using the Visual Analogue Scale (VAS). A 100mm ruler with a visual depiction of pain levels (smiling face to frowning face) was used. Patients were told their previous pain scores at each assessment. Knee function was evaluated using Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [28]. Both evaluations were performed before the injection and at first, third, and sixth-month follow-ups. All complications and adverse effects were monitored during the study period. At least 3-points reduction in VAS and 17-points reduction in WOMAC were accepted as a clinically meaningful improvement considering the minimal important change (MIC) reported in previous studies [29,30].

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Base v.23 for Windows. Descriptive statistics were reported as mean and standard deviation, frequency distribution, median, minimum and maximum values. The Shapiro-Wilk test was employed to examine the normality assumption. Normally distributed variables were analyzed with the student t-test, and non-normally distributed variables were analyzed with the Mann-Whitney-U-test. Categorical variables were compared with the Chi-square test. Repeated measures within the same group were compared with repeated measures of ANOVA. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The trial enrolled 60 patients who met the inclusion criteria, 30 of whom were equally assigned to each group. Figure 1 illustrates the progression of patients during the trial. None of the patients

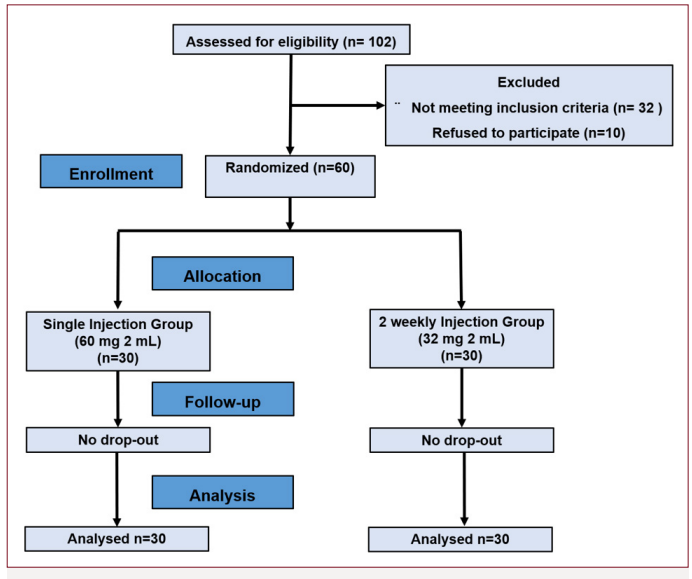

Figure 1. Flow diagram of the patients.

were lost in follow-up; thus, 60 patients were available for the final analysis. The two groups had no significant variations in baseline patient characteristics (Table 2).

Table 2. Demographic and baseline clinical characteristics of the patients

Variables	Single Dose (n=30)	Two-weekly (n=30)	p
Age (years±SD)	56.6±8.9	58.4±8.1	0.400
Sex (n/%)			0.191
Male	10 (33.3%)	6 (20%)	
Female	20 (66.6%)	24 (80%)	
Side			0.398
Right	14 (46.6%)	16 (53.3%)	
Left	16 (53.3%)	14 (46.6%)	
Height (cm±SD)	165.5±8.8	161.3±7.7	0.059
Weight (kg±SD)	83.3±13.8	80.7±15.1	0.497
BMI (kg/m^2±SD)	30.4±5.0	30.9±5.1	0.702
OA Grade (n / %)			0.119
Grade II	27 (90%)	30 (100%)	
Grade III	3 (10%)	0 (0%)	
Initial VAS (points±SD)	5.8±1,3	5,3±1.3	0.113
Initial WOMAC (score±SD)	47.6±24.2	51.3±19.5	0.517

SD: standard deviation; BMI: body mass index; OA: Osteoarthritis; VAS: visual analog scale; WOMAC: Western Ontario and McMaster University Osteoarthritis Index.

Table 3. Changes in the VAS during the study period

Variables	Single Dose (n=30)	Two-weekly (n=30)	p
VAS Initial	5.8±1.3	5.3±1.3	0.113
VAS 1st month	3.5±1.4	3.2±0.9	0.249
VAS 3rd month	3.3±1.5	3.4±1.2	0.789
VAS 6th month	3.2±1.3	3.6±1.5	0.294
Repeated ANOVA, p	**0.001**	**0.001**	
MIC			0.217
Δ (Initial-Final) VAS<3 points	15	19	
Δ (Initial-Final) VAS ≥ 3 points	15	11	

VAS: visual analog scale; ANOVA: Analysis of variance; MIC: Minimal important change.

Repeated measurements of VAS showed a significant reduction throughout the follow-up in both groups (p=0.001) (Table 3). There was no significant difference between groups at each time point. Similarly, repeated measurements of WOMAC showed a significant improvement throughout the follow-up in both groups (p=0.001). However, the WOMAC score in the sixth month was significantly better in the single-dose HA injection group (Table 4). Considering MIC for VAS and WOMAC, both groups were similar (p=0.217 and p=0.500, respectively) (Fig. 2). An adequate pain reduction could not be achieved in more than half of the patients (56.6%), and almost half (45%) did not have a clinically significant increase in knee function at the final follow-up, according to MIC values.

No significant complications, such as septic arthritis or allergic reactions, were recorded during the study. Two patients in each group reported increased pain that immediately started following the injection and lasted one week after. All of these patients were obese patients with a wide knee diameter. This minor complication might be related to the difficulties during the injection. Since all injections were performed using anatomic landmarks by palpation, the needle might have penetrated the cartilage and subchondral bone, resulting in pain. No joint effusion or infection was observed in any of the patients. The total cost of the single injection treatment, including doctor visits, intraarticular injections and disposables, was 64 USD per patient, while the two weekly injection treatments cost 100 USD per patient in the authors' country.

Table 4. Changes in WOMAC score during the study period

Variables	Single Dose (n=30)	Two-weekly (n=30)	p
WOMAC Initial	47.6±24.2	51.3±19.5	0.517
WOMAC 1st month	32.2±18.0	35.5±13.4	0.416
WOMAC 3rd month	27.8±14.6	31.9±13.5	0.266
WOMAC 6th month	24.5±15.0	34.3±16.3	0.019
Repeated ANOVA p	**0.001**	**0.001**	
MIC			0.500
Δ (Initial-Final) WOMAC<17 points	13	14	
Δ (Initial-Final) WOMAC ≥ 17 points	17	16	

WOMAC: Western Ontario and McMaster University Osteoarthritis Index; ANOVA: Analysis of variance; MIC: Minimal important change.

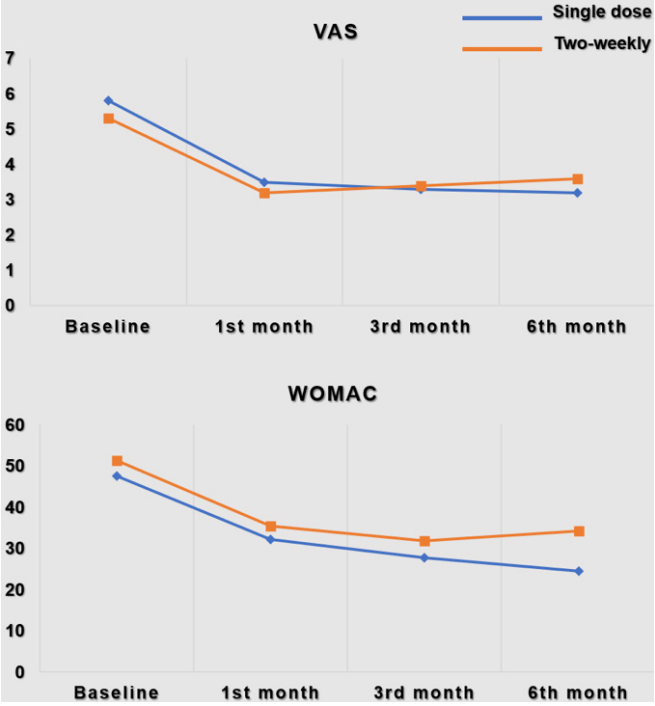

Figure 2. Baseline and follow-up VAS and WOMAC scores of the groups. The blue line designates the single-dose group, and the orange line designates the Two-weekly group.

DISCUSSION

This randomized clinical trial compared the effectiveness of a single dose versus two weekly injections of sodium hyaluronate in treating mild to moderate knee OA symptoms by measuring pain and knee function. The single-dose injection was 3% sodium hyaluronate at a volume of 2 ml and 60 mg, while the two weekly injections were 1.6% sodium hyaluronate at a volume of 2 ml and 32 mg each. The results of this study indicate that both regimens significantly decreased pain and improved knee function following the HA injection. The WOMAC score in the sixth month was significantly better in the group receiving a single HA injection dose. No significant complications that needed secondary intervention were observed. However, there was no significant difference between the groups regarding the MIC values for both VAS and WOMAC. An adequate pain reduction could not be achieved in more than half of the patients (56.6%), and almost half (45%) did not have a clinically significant increase in knee function at the final follow-up. Based on the findings in this study, a single-dose HA (60 mg, 2 ml) injection is not more effective in reducing pain and improving function in patients with knee OA compared to two weekly (32 mg, 2 ml) injections. Thus, the hypothesis was refuted. Nevertheless, the overall cost of treatment was cheaper in the single-dose injection group. Both regimens cannot sufficiently control pain and improve function; thus, the role of viscosupplementation in symptomatic knee OA is questionable.

Current research on the effectiveness of a single high-dose HA injection versus multiple lower-dose injections is controversial (Table 5). Some studies have found that a single high-dose injection is more effective at reducing pain and improving joint function than multiple lower-dose injections [15,20,23], while other studies have found no significant differences between the two regimens [17,19,21,22]. Furthermore, various other studies support consecutive injections to achieve sufficient pain control and improve function [11,12,16,18].

Conrozier et al. [15] reported on a randomized trial in 100 patients with knee OA, which aimed to assess five different dosing regimens of hylan G-F 20. Results showed that all treatment regimens resulted in statistically significant improvements in WOMAC index and VAS, with the single 6 mL injection and the three times 2 mL injections showing the most remarkable mean improvements. They proposed that a single 6 mL injection appears to be good, and this regimen could be developed as an alternative to multiple injections considering the risk/benefit ratio. Estades-Rubio et al. [20] compared the effectiveness and treatment cost of stabilized hyaluronic acid (NASHA) in a single injection with standard HA preparations in five injections. Results showed that NASHA was more effective than standard preparations in reducing pain, and there was a reduced need for analgesia during the six-month follow-up. Finally, Huang and Tsai [23] compared the efficacy and safety of a single injection of Cross-linked Hyaluronic Acid Platform Hyaluronan (CHAP-HA) with three injections of linear hyaluronan in knee OA patients. Results showed that CHAP-HA significantly improved VAS pain scores compared to linear-HA at week 26, with no significant differences in adverse events between the groups. Overall, these studies suggest that single-dose HA injections are effective and well-tolerated in reducing pain and improving function in knee OA patients.

Besides the abovementioned studies, four other clinical trials could not show any difference between single versus multiple injections [17,19,21,22]. Zhang et al. [17] compared the single versus multiple injections of two HA formulations, single-dose 3 mL high molecular weight hyaluronic acid (HMWHA), and five-weekly 2.5 mL low molecular weight hyaluronic acid (LMWHA), in 349 patients. The results showed that both treatments were efficacious, safe, and well-tolerated. Specifically, a single injection was non-inferior to five injections over 18 and 26 weeks for pain, physical function, global self-assessment, and

Table 5. Previous clinical trials that compared single versus multiple hyaluronic acid injection knee OA in the current literature

Author	Year	Design	# Patients	Regimen	Injection	Follow-up (weeks)	Recommendation
Conrozier et al. [15]	2009	RCT	Group 1: 20	Single dose	6 mL HMWHA	24	A single-dose regimen. might be recommended over multiple injections
			Group 2: 20	Single dose	4 mL HMWHA		
			Group 3: 19	Two-weekly	4 mL HMWHA		
			Group 4: 20	Three-weekly	4 mL HMWHA		
			Group 5: 19	Three-weekly	2 mL HMWHA		
Zoboli et al. [16]	2013	RCT	Group 1: 53	Single dose	6 mL IMWHA	12	No significant difference between the groups. Better pain control in three-weekly injections
			Group 2: 52	Three-weekly	2 mL IMWHA		
Zhang et al. [17]	2015	RCT	Group 1: 167	Single dose	3 mL HMWHA	26	No significant differences. between the groups
			Group 2: 165	Five-weekly	2.5 mL LMWHA		
Dıracoglu et al. [18]	2016	RCT	Group 1: 20	Single dose	4 mL IMWHA	24	Similar WOMAC Better pain in three-weekly injections
			Group 2: 20	Three-weekly	2.5 mL LMWHA		
Ha et al. [19]	2017	RCT	Group 1: 129	Single dose	3 mL XLHA	12	No significant differences between the groups.
			Group 2: 137	Three-weekly	2 mL HMWHA		
Estades-Rubio et al. [20]	2017	RCT	Group 1: 27	Single dose	3 mL HMWHA	26	Single dose is better than multiple injections
			Group 2: 27	Five-weekly	2.5 mL IMWHA		
Bahrami et al. [21]	2020	RCT	Group 1: 39	Single dose	3 mL HMWHA	24	No significant differences. between the groups
			Group 2: 40	Three-weekly	2 mL LMWHA		
Suppan et al. [22]	2020	RCT	Group 1: 62	Single dose	5 mL IMWHA	52	No significant differences. between the groups
			Group 2: 63	Three-weekly	2.5 mL IMWHA		
Huang and Tsai [23]	2021	RCT	Group 1: 58	Single dose	3 mL HMWHA	26	A single dose is better than multiple injections
			Group 2: 56	Three-weekly	2 mL LMWHA		
Current Study	2024	RCT	Group 1: 30	Single dose	2 mL IMWHA	26	No significant differences between the groups regarding MIC
			Group 2: 30	Two-weekly	2 mL IMWHA		

RCT: Randomized clinical trial, LMWHA: Low molecular weight hyaluronic acid, IMWHA: Intermediate molecular weight hyaluronic acid, HMWHA: High molecular weight hyaluronic acid.

knee stiffness. Ha et al. [19] compared the efficacy and safety of a single injection of cross-linked hyaluronate (XLHA) with three weekly injections of linear HMWHA in patients with knee OA. Two hundred eighty-seven patients were randomized to receive either XLHA or HMWHA injections. The study found that a single injection of XLHA was non-inferior to three weekly injections of linear HMWHA in reducing weight-bearing pain, with no significant differences in secondary endpoints and mild adverse events reported. Bahrami et al. [21] reported that a single injection of a cross-linked high-molecular-weight HA was equally effective as multiple linear low-molecular-weight HA (LMW-HA) injections in reducing pain and improving function during the two and 6-month follow-up periods. Similarly, Suppan et al. [22] found that a single large dose of intra-articular HA injection and three repeated smaller doses had comparable effectiveness over 12 months, but the single-dose regimen was associated with lower total treatment costs.

Contradictory findings are also reported in systematic review and meta-analysis studies investigating HA injection dosing regimens. Concoff et al. [12] reviewed the clinical trials on the effectiveness and safety of HA injections compared to placebo saline injections for knee OA. The review revealed that 2-4 injections of HA provided the most significant pain relief compared to saline injections, while single HA injections were not effective. Saline injections were generally safe, although five or more injections were linked to an increased risk of treatment-related adverse events. McElheny et al. [13] found no consistent difference in patient-reported outcomes between single and multiple-injection formulations, and single-injection formulations were more cost-effective and less inconvenient for patients. Another systematic review that aimed to assess the long-term effectiveness and safety of hylan G-F 20 injections for knee OA found similar efficacy of single or 1-3 weekly injections [14]. In contrast, Altman et al. [11] concluded that repeated courses of treatment provided sustained control of pain or further reduced it throughout the follow-up.

Some authors argue that HA injections are ineffective in treating symptomatic knee OA. In a recent systematic review and meta-analysis of randomized trials evaluating the effectiveness and safety of viscosupplementation for knee OA treatment, it is reported that viscosupplementation leads to a slight reduction in knee OA pain compared with placebo. The difference was less than the minimal clinically important between-group difference, and it is also associated with an increased risk of serious adverse events compared with a placebo [31]. Another meta-analysis concluded that viscosupplementation has a minimal or non-existent positive effect on pain and function in patients with knee OA and poses an increased risk of serious and local adverse events [32]. Similarly, the findings of our study confirm these results, although no significant adverse reactions were seen. Patients in both groups did not significantly benefit from treatment. The recent guideline on managing knee OA reported by the American Academy of Orthopaedic Surgeons (AAOS) also recommended against the routine use of HA in patients with knee OA [33].

There are some strengths and limitations of this study. A limitation of this study is the relatively small sample size, which may limit the generalizability of the results. In addition, the lack of blinding of both patients and clinicians could introduce bias, as expectations of treatment efficacy could influence the reported results. The study also did not include a placebo group, which may have provided a clearer understanding of the effects of HA injections compared to no treatment. Finally, variability in patient compliance and response to pain assessment tools such as VAS and WOMAC may have influenced the results. Despite these limitations, this trial has notable strengths. It is a randomized controlled trial with a robust design, including well-defined inclusion and exclusion criteria, which increases the reliability of the results. The comparison of two different HA injection regimens provides valuable evidence for clinical decision-making in the treatment of knee OA. In addition, the study's adherence to standardized radiological and functional assessment methods supports the consistency and validity of the results, providing a meaningful contribution to the ongoing debate on the efficacy of single versus multiple HA injections in the treatment of OA.

CONCLUSION

In conclusion, this study compared the effectiveness of a single dose versus two weekly injections of sodium hyaluronate in treating mild to moderate knee OA symptoms. Both regimens might provide a slight reduction in pain and improvement in knee function without reaching clinical significance. Half of the patients did not achieve adequate pain reduction and had a clinically significant increase in knee function. Therefore, the study suggests that the effectiveness of viscosupplementation in treating symptomatic knee OA is questionable and uncertain. Further studies might focus on selecting the patients who will benefit from the viscosupplementation in knee OA.

DECLARATIONS

Ethics Committee Approval: The Antalya Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 07.11.2019, number: 24/2).

Author Contributions: Idea/Concept – AB, MU; Design – AB, MU; Control/Supervision – AB, MU; Data Collection and/or Processing – AB, MU, MBE; Analysis and/or Interpretation – MU, OFE; Literature review – MBE, AB; Writing – AB, MU, MBE, OFE; Critical Review – AB, MU, MBE, OFE; References and fundings – AB, MU, MBE, OFE; Materials – AB, MU, MBE

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

Conflict of Interest: The authors had no conflict of interest to declare.

Informed Consent: Written informed consents were provided by the participants.

Use of AI for Writing Assistance: The authors declared that they had not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Peer-review: Externally peer-reviewed.

ABBREVIATIONS

AAOS - American Academy of Orthopaedic Surgeons

CHAP-HA - Cross-linked hyaluronic acid platform hyaluronan

HA - Hyaluronic acid

HMWHA - High molecular weight hyaluronic acid

IMWHA - Intermediate molecular weight hyaluronic acid

LMWHA - Low molecular weight hyaluronic acid

MIC - Minimal important change

NASHA - stabilized hyaluronic acid

OA – Osteoarthritis

PACS - Picture archiving and communication systems

PRP - Platelet-rich plasma

RCT - Randomized controlled clinical trial

VAS - Visual analog scale

WOMAC: Western Ontario and McMaster University Osteoarthritis Index

XLHA - Cross-linked hyaluronate

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