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THE SAFETY AND EFFICACY OF SINGLE INTRA-ARTICULAR HYALURONIC ACID INJECTION IN PATIENTS WITH KNEE OSTEOARTHRITIS: A PROSPECTIVE STUDY

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ABSTRACT

Introduction*: To evaluate the effectiveness and safety of viscosupplementation with intra-articular hyaluronic acid injection (IA-HA) in patients with knee osteoarthritis (OA).*

Materials and methods*: This prospective study was carried out among the patients with grade II and III (Kellgren Lawrence classification) osteoarthritis of the knee attending outpatients clinic from March 2019 to January 2020. Patients, who did not achieve remission of pain despite receiving the first-line treatment for gonarthrosis were included in the study. A single dose of HA was injected into the target knee joint. Clinical evaluation was done using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the short form-36 questionnaires (SF-36 v2) at baseline, 3 months and 6 months by an independent evaluater.*

Results*: A total of 67 patients with knee OA enrolled and completed the study. Statistically significant improvements from baseline to 3 months were observed in the total WOMAC score that remained significant until the end of 6 months. Most of the domains of SF-36 also showed significant improvement from baseline to 3 and 6 months. No patient reported adverse effects during the study.*

Conclusion*: Among the patients within this study, treatment with single IA-HA injection improved all domains of WOMAC score and the quality of patients' life starting from week 12 that was sustained until 6 months at least. These findings suggest 90 mg/3 mL HA injection to be an effective and safe alternative in improving pain and functional status of patients with gonarthrosis.*

Keywords: *Intra-articular injection, gonarthrosis, non-operative treatment, viscosupplementation.*

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Introduction

Osteoarthritis (OA) is a progressive and degenerative joint disease that leads to physical disability in the aging population[1]. According to the World Health Organization (WHO), 9.6% of men and 18.0% of women (age >60 years) have symptomatic OA, worldwide[2]. Prevalence of symptomatic knee OA increases with age and is estimated to double by 2040 in Asians ≥65 years[3].

Treatment goals for managing knee OA as recommended by the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee include alleviation of pain, preserving and improving joint function, providing functional independence, and increasing the quality of life[4]. Non-pharmacological management such as lifestyle modifications, physical therapy and pharmacological therapy with analgesics and anti-inflammatory medications are often ineffective in achieving these goals, and lead to residual symptoms[5].

Reductions in the concentration and quality of naturally producing hyaluronic acid (HA), which provides adequate elasticity and viscosity to the synovial fluid, is one of the critical pathophysiological

changes in OA[5]. Viscosupplementation of the joint may restore physiological and rheological states of arthritic joints, and help alleviate pain. Intra-articular HA (IA-HA) injections have been used for the same in patients with mild-to-moderate OA, and in certain subgroups of severe OA with comorbidities or in patients with poor response to first-line treatment[4,6].

Typically, treatment with IA-HA consists of 3 to 5 injections at weekly intervals. The HA used in these products differs mainly in their origin, concentration, and dosing regimens. However, since 2004, alternative regimens of single injections have also been developed as an alternative to multi-injections that dispense the same amount of HA[7]. Using single injections could improve feasibility, and help avoid any discomfort associated with multiple injections[8]. Several randomized trials, open-label studies and meta-analyses have shown advantages of single IA-HA injection over multi-injection regimens[7-9].

In the present study, we present results from a prospective study evaluating efficacy and safety of a single dose of 90mg/3ml IA-HA product in patients with grade II and III knee OA.

Materials and methods

Study design

This prospective, single-center, single-arm, open-label, study was conducted at Istanbul Medeniyet University Faculty of Medicine, Goztepe Prof.Dr.Süleyman Şahin State Hospital, Istanbul, Turkey from March 2019 to January 2020. This study was approved by the institutional ethics committee and was conducted in accordance with the ethical standards of the Declaration of Helsinki, ISO 14155, and International Conference on Harmonization's Good Clinical Practice guidelines. All patients signed informed consent prior to their enrollment in the study. The Ethical Committee Approval no: 2018/0489 and Clinical Trials code: NCT04577521.

Patients

Patients with OA of the knee who did not achieve remission of pain despite receiving the first-line treatment for gonarthrosis including nonsteroidal antiinflammatory drugs medication, activity modification, and ice, were included in the study. Inclusion criterias were as follows: patients ≥18 years of age with a diagnosis of knee OA as per the American College of Rheumatology (ACR) criteria (10), diagnosis of Kellgren Lawrence grade II or III OA of the knee on weightbearing standard knee anteroposterior, and lateral plain radiographs, consistent symptoms of knee OA (joint pain, crepitus, swelling, effusion alone or with the symptoms) for at least 3 months before screening; willingness to discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics. However, patients were allowed to use only acetaminophen or aspirin as a rescue pain medication during the study period. All patients have abstained from medications 24 h before the study visit. Patients with bilateral knee pain, the more painful knee was considered as the target knee. Patients with secondary knee OA as per the ACR criterias, history of surgery or trauma of the target knee, a need for pharmacological treatment for OA of the joints other than target knee, and those who received IA-HA in the last 6 months and /or steroids or articular lavage in the target knee, or glucosamine sulfate, chondroitin sulfate and diacerein in the last 3 months, were excluded. Patients with neurological deficits in lower extremities, primary inflammatory joint disease, intra-articular tumors or any severe systemic disease(s) or allergy, or hypersensitivity to HA, and those who participated in any study in the last 3 months were also excluded from the study.

Treatment procedure

The study included a total of four visits, one each for clinical examination and treatment/ injection, and two for post-treatment follow-up visits at 3 and 6 months (Fig. 1).

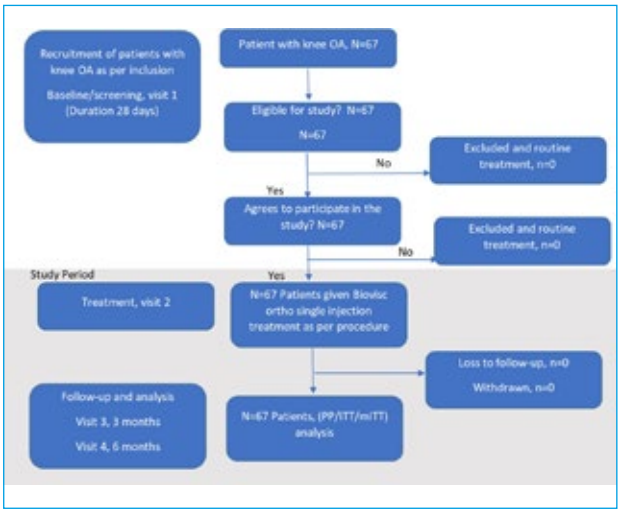

Fig. 1: Flow chart of the study.

The study device consisted of a prefilled syringe containing 90 mg/3 mL of IA-HA (BioVisc Ortho Single, Biotech Vision Care Pvt Ltd., Ahmedabad, India) that is an injectable-grade HA from a biofermentation origin. Biovisc ortho single

prefilled syringes are intended for single-use only, and the entire content of the syringe was injected into the target joint. All patients received an IA-HA injection during the treatment visit. The aseptic technique was followed while handling the syringe and administration.

Assessments and outcomes

A complete medical history was assessed at screening and physical examination was performed at screening, treatment, and at follow-up visits at 3 and 6 months.

Clinical efficacy of IA-HA was evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Changes from baseline to 3 and 6 months in the WOMAC score was considered as a primary endpoint. The WOMAC score is one of the highest-performing patient-reported outcome measures for knee and hip OA, in terms of reliability, validity, responsiveness, and interpretability, and is recommended by the United States Food and Drug Administration (US-FDA), European Medicines Agency (EMA) and other working groups[11-16]. It is a validated pain scoring system that consists of a health-status-measure questionnaire of twenty-four questions that consist of three subscales (pain, stiffness, and physical function). It is measured on a scale of 0-100 mm where a lower score represents lower pain and a higher score represents higher pain. Changes in the quality of life from baseline to 3 and 6 months of patients were also assessed using the Short Form-36 questionnaire (SF-36).

Safety of single IA-HA injection was assessed by recording adverse effects (AE) throughout the 24 h post-dose period and at all follow-up visits.

Statistical analysis

The sample size was calculated assuming the minimal perceptible clinical improvement (MPCI) of 9.7 mm (standard deviation of 22 mm) on the WOMAC pain scale. Assuming the paired difference of -2.00 from baseline to 6 months in the WOMAC score, at least 50 patients were required to achieve 90% power at a 5% level of significance. Considering a 20% probability of loss to follow-up, a total of 67 patients were required to be enrolled in the study.

All participants who signed informed consent and received at least one dose of the assigned medication were considered as the safety population. Intent-to-treat (ITT) population included those who received at least one dose of the assigned medication and had at least one post-treatment baseline visit. Per-protocol (PP) population included those participants who completed the study in compliance with the protocol without any major deviation. Continuous and quantitative variables were summarized using descriptive statistics and were compared using Student's t-test or Wilcoxon signed-rank test as applicable. Categorical data were presented as frequency count (n) and percentages (%) and were compared using the χ^2 test or Fisher's exact test. Statistical analysis was performed using SAS (SAS Institute Inc., Cary, NC, USA, version 9.4) software. p-value which was less than 0.05 was considered to reflect the statistical significance.

Results

Patient disposition

All 67 patients who enrolled, received Biovisc ortho single injection. No patient was discontinued or lost to follow-up, and all patients completed the study. No protocol deviations were reported, and all 67 patients were analyzed in the PP, ITT, and safety population. Patient demographics and clinical characteristics are presented in Table 1.

Characteristics	N (%) or Mean ± SD
Age, years	64.1 ± 8.0
BMI, kg/cm^2	32.1 ± 5.8
Caucasian ethnicity	67 (100)
Gender	
Female	48 (71.6)
Male	19 (28.4)
Affected knee	
LEFT	42 (62.7)
RIGHT	25 (37.3)
Primary diagnosis	
Crepitus on active motion	49 (73.1)
Morning stiffness	34 (50.7)
Pain	67 (100.0)
Swelling	43 (64.2)
Clinical history	
Diabetes mellitus	19 (28.4)
Hypertension	36 (53.7)
Hyperthyroidism	4 (6.0)
Hyperlipidemia	8 (11.9)
Other cardiovascular disorder	5 (7.5)
Asthma	1 (1.5)

Table 1: Demographic and clinical characteristics of patients.

Data are presented as N(%) or mean ± SD; BMI: body mass index

Efficacy

The mean total WOMAC score at baseline was 55.3 ± 14.6, which reduced to 48.3 ± 14.5 at 3 months (mean reduction: -7.0 ± 4.4, p<0.0001), which further reduced to 44.1±14.7 at 6 months

(mean reduction: -11.2 ± 6.4, p<0.0001) as shown in Fig. 2.

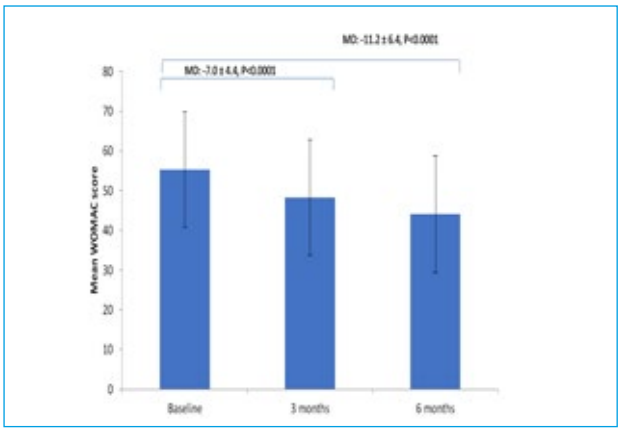

Fig. 2: Improvement in the total Womac score.

Similar trends in improved WOMAC subscores for pain, stiffness, and physical function were also observed (Table 2). Overall, the minimum clinically important difference (MCID) of 10 points in the total WOMAC score was observed in 29% of patients at 3 months and by 50% of patients at 6 months.

	WOMAC score of the patients		
	Mean ± SD	Mean difference ± SD from baseline	P value
WOMAC score-Pain			
Baseline	12.9 ± 3.9		
3 months	11.4 ± 3.8	-1.5 ± 1.3	<.0001
6 months	10.6 ± 3.6	-2.4 ± 1.9	<.0001
WOMAC score-Stiffness			
Baseline	2.1 ± 2.5		
3 months	1.8 ± 2.2	-0.3 ± 0.8	0.0007
6 months	1.6 ± 2.1	-0.5 ± 0.9	<.0001
WOMAC score-Physical function			
Baseline	40.2 ± 10.1		
3 months	35.1 ± 10.0	-5.1 ± 3.2	<.0001
6 months	31.9 ± 10.3	-8.3 ± 4.7	<.0001

Table 2: WOMAC sub-scores of patients at baseline, 3 and 6 months.
WOMAC: Western Ontario and McMaster universities osteoarthritis index; SD: standard deviation

Pain relief and improved physical function were reflected in the quality of life of patients that was determined by the SF-36 questionnaire. Most of the domains of the questionnaire, including pain, physical function, social function, mental health, role limitation-mental, and vitality showed significant improvement from baseline to 3 and 6 months (p<0.001); however, no significant improvement in domains for role limitation-physical and general health perceptions was observed (Table 3).

Safety

No patient reported AE during the study was seen. Device failure or device malfunctioning cases were also not observed throughout the study.

	SF-36 Scores of patients		
	Mean ± SD	Mean difference ± SD from baseline	P value
SF-36 (Physical function)			
Baseline	33.3 ± 13.2		
3 months	39.3 ± 13.3	6.0 ± 6.2	<.0001
6 months	42.2 ± 14.23	9.0 ± 8.0	<.0001
SF-36 (Social function)			
Baseline	51.6 ± 25.0		
3 months	56.8 ± 24.5	5.2 ± 9.5	<.0001
6 months	61.6 ± 23.8	10.0 ± 13.3	<.0001
SF-36 (Mental health)			
Baseline	60.8 ± 12.6		
3 months	63.1 ± 12.7	2.3 ± 3.4	<.0001
6 months	64.4 ± 12.2	3.6 ± 4.2	<.0001
SF-36 (Pain)			
Baseline	34.7 ± 17.6		
3 months	45.2 ± 17.0	10.5 ± 10.8	<.0001
6 months	49.8 ± 19.0	15.1 ± 14.5	<.0001
SF-36 (Role limitation - Mental)			
Baseline	22.7 ± 15.4		
3 months	15.3 ± 16.6	-7.4 ± 13.9	<.0001
6 months	10.8 ± 15.6	-11.8 ± 15.9	<.0001
SF-36 (Energy/Vitality)			
Baseline	45.1 ± 15.5		
3 months	48.7 ± 15.1	3.6 ± 5.5	<.0001
6 months	50.7 ± 15.4	5.6 ± 7.4	<.0001
SF-36 (Role limitation - Physical)			
Baseline	0.4 ± 3.1		
3 months	0.4 ± 3.1	0.0 ± 0.0	
6 months	0.7 ± 4.3	0.4 ± 3.1	0.3210
SF-36 (Health perceptions)			
Baseline	44.9 ± 13.5		
3 months	45.3 ± 13.5	0.4 ± 2.2	0.1672
6 months	45.2 ±13.7	0.3 ± 2.1	0.2512

Table 3: SF-36 Score of patients at baseline, 3 and 6 months.
SF-36: Short Form Health Survey questionnaire; MD: mean difference; SD: standard deviation

Discussion

The present prospective, single-center, single-arm, open-label, observational study showed improvements in all WOMAC scores and most of the SF-36 domains at 3 months that were consistent for at least 6 months. These results indicate that a single dose of 90mg/3ml IA-HA could be an effective and reliable treatment option for patients with knee OA.

Viscosupplementation has been recommended for treating patients with mild or moderate knee OA and in those with poor response to first-line treatment[4,6,17]. Benefits of IA-HA in reducing pain and improving functional status have been reported in several trials[18-21]. Besides, its role as a local treatment in OA secondary to chronic inflammatory arthritis was also reported in a systematic review by De Lucia et al. in 2020[22]. The clinical benefit of IA-HA on knee OA may rely on two aspects; first, mechanical viscosupplementation of the joint allows lubrication and shock absorption, and the second, it induces endogenous collagen production that persists for long-term (about six months) re-establishing joint homeostasis[23,24]. A recent meta-analysis of 28 studies by Vincent et al. also suggested that single-injection produces the results similar to multi-injections of IA-HA in terms of pain relief in treating knee OA[7].

The present study is consisted with the literature in terms of the mean age, the mean body mass index and gender (Table 1)[7]. All the patients included in this study suffered from knee

pain, and the other most common complain was about range of motion. The reduction in WOMAC stiffness score and WOMAC function score are in line with previous studies[25,26]. Keary et al. reported significant reduction of WOMAC stiffness score and function score at 6 month after single IA-HA injection (48mg/10ml[25]. Similarly, Sun et al. found significant improvements in WOMAC stiffness score and function score at 3, and 6 months after 60mg/3ml and 48mg/3ml treatment[27].

Several open-label studies have evaluated the effectiveness of single-injection IA-HA products in patients with knee OA. Improvement in the WOMAC score was a primary endpoint in these studies but its definition varied slightly across the studies. In the LOBRAS study by Keary et al., WOMAC scores were improved by 24-39% initiating from week 12 until week 52 with a single IA-HA injection (48mg/10ml)[25]. The rate of treatment-related AEs was 5.3%[25]. In a study by Baron et al., an improvement from baseline in the WOMAC pain index was 28% following 60 days post-treatment with single IA-HA (75mg/3ml), while single-injection of 48mg/10ml IA-HA showed >20% improvement in all WOMAC domains starting from week 12[8]. Our results are consistent with the improvements reported in the WOMAC score in these studies. Significant improvement from baseline was observed in all domains of the score with a total improvement of 20% at 6 months after the administration of a 90mg/3ml single injection. Although no change was observed in the disease grade, no need for surgery in patients with knee OA. Improvement in the WOMAC pain score was also reflected by concurrent enhancement in the quality of life as shown by improved SF-36 scores. In our study, there was no withdrawal or loss to follow-up, and no AEs were reported throughout the study period. This indicated that the treatment was reliable. Our results support the use of 90mg/3ml single as a safe and effective alternative for patients who may want an alternative treatment modality or may not be candidates for partial or total knee replacement.

Our results are also consistent with those from randomized studies of single-injection IA-HA. Sun et al. compared the efficacy and safety of a single IA-HA injection of cross-linked hyaluronan with a single injection of 48mg/10ml in patients with knee OA. The study reported improvements in all domains of WOMAC scores at 1, 3, and 6 months after 60mg/3ml and 48mg/3ml treatment[26]. However, the development of joint effusion occurred within a week of injection with 60mg/3ml (5%) or 48mg/3ml (13.6%) in a few patients[26].

In our study, no patients have reported the development of joint effusion. In a study by Petterson et al., 52.5% of patients showed at least 50% improvement and ≥20 mm of absolute improvement from baseline in the WOMAC pain score with a single-injection IA-HA device (88mg/4ml) without any serious AEs[27]. Similarly, Kotevoglu et al. reported improvement in total pain score with single IA-HA injection (16mg/2ml and 30mg/2ml) from baseline to 6 months ($p<0.05$)[28], and Uçar et al. also showed these injections were effective in both young and advanced-aged patients with OA in regards to pain and functional status over a short-term period[29]. A minimum clinically important difference for the total WOMAC score is reported to be 10 at 1-year, which was achieved by more than 50% of patients at 6 months in our study. Biovisc ortho single (90mg/3ml) offers the advantage of treatment with a single injection that could improve patient adherence and is convenient for both patients and physicians. It could be effective, and a minimally invasive treatment alternative for patients treated for symptoms of knee OA.

Several studies have reported reduced intake of analgesics including NSAID using IA-HA but we did not assess the use of rescue pain medications in our study. Considering the similar efficacy results, a similar decrease in analgesic use can be expected from treatment with Biovisc[8]. Recently, treatment with a single IA-HA injection was shown to provide a similar improvement in knee pain, function, and a range of motion compared to corticosteroid triamcinolone at 6 months[30]).

Overall, this open-label study was designed and conducted according to the the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee recommendations for managing knee OA. The major limitation of our study was the lack of a control group (either active or placebo); on the other hand, the strengths are an adequate number of patients, any loss at the control visit, and enough follow-up duration.

In conclusion, treatment with single-dose Biovisc (90mg/3ml) IA-HA injection improved all domains of WOMAC score and the quality of life of patients starting from week 12 and sustained until at least 6 months. These findings show that Biovisc IA-HA injection could be an effective and safe alternative in improving pain and functional

mobility in patients with Kellgren and Lawrence grade II or III knee OA.

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