



Impact of Intra-articular Infusion of Hyaluronic Acid on Gait Pattern of Patients with Knee Osteoarthritis in Tehran, Iran

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Keywords

Hyaluronic acid; Osteoarthritis; Gait analysis; Knee Injury and Osteoarthritis Outcome Score

Abstract

Background: Intra-articular hyaluronic acid (IAHA) injection is one of the treatments of knee osteoarthritis (KO) that increase synovial fluid elasticity and viscosity, therefore decrease pain and increase function. However, its effect on the patient's gait is not clear objectively. The purpose of this study is to examine the impact of IAHA injection on gait pattern in patients with KO.

Methods: After receiving informed consent of patients, the demographic questionnaire and the Knee Injury and Osteoarthritis Outcome Score (KOOS) were filled by them. Knee range of motion (ROM) and gait pattern were measured by goniometer and Zebris gait analyzer made in Germany. IAHA injection was performed three times weekly for fifteen days. One week, one month, three months, and six months after the last injection, KOOS, the knee ROM, and gait were examined again.

Results: Stride length, stride time, cadence, gait

velocity, quality of life (QOL), and knee ROM showed improvement after the injection ($P < 0.05$).

Conclusion: Intra-articular infusion of hyaluronic acid (HA), by increasing the elasticity and viscosity of the fluid in the joint, leads to pain reduction and improvement in gait parameters and QOL in patients with KO.

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Introduction

Osteoarthritis (OA) is a degenerative disease of the synovial joints that affects the articular cartilage and results in the loss of articular cartilage and alteration in other tissues, including synovial membrane inflammation, articular capsule thickening, muscle weakness, and new bone formation.^{1,2} It is seen in all age

groups and is present in 6% of adults. Statistics also show that it affects about 30-40 percent of people aged 65 years.³ OA is one of the major causes of decreased daily activities and poor quality of life (QOL) in the elderly.⁴

Knee OA (KO) is one of the most common musculoskeletal problems,^{3,5,6} which decreases patient function due to arthritis pain, stiffness, and movement limitation.^{5,6} It also affects not only the intra-capsular tissues, but also the tissues surrounding the joint, including the ligament, capsule, tendon, and muscles,⁷ leading to a marked decrease in muscle strength and deep joint sensation.⁸⁻¹⁰ Pain when walking, movement limitation, and pain in full knee flexion are also common symptoms.^{11,12} The angular velocity and range of motion (ROM) of the knee during gait are significantly reduced in these patients,¹³ thus, affecting the patient's gait pattern.¹⁴

Gait analysis, considered as an adjunct to physical examination and other diagnostic methods to treat motor problems, can provide accurate evidence of the cause and effect of deformities on human physiological activity. Gait analysis can identify primary motor problems from problems caused by other causes and can be used to treat patients with severe and moderate motor problems, especially in those undergoing surgery.¹⁵

Interventions that can be performed on motor problems include the administration of therapeutic exercises, orthoses, medications (systemic, local, internal), and surgery. Being aware of the biomechanics of normal movement and pathologies of gait using gait analysis is essential while applying useful techniques for the treatment of patients.¹⁵

Knee OA can cause debilitating pain, dysfunction, and weakness of the muscles surrounding the joint following non-use of organs in the long run, which highlights the need for improved therapeutic methods. There are various treatments for KO that include oral medications [analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)], intra-articular corticosteroids (in cases of effusion and inflammation), topical ointments such as

capsaicin, exercise, physiotherapy, weight-adjustment braces, and knee arthroplasty surgery, with each having limited efficacy in reducing pain. In the meantime, surgical complications and excessive costs are imposed on the patient in cases such as arthroplasty.

Disease-modifying drugs (DMDs) such as cartilage-protective drugs have been considered, and this treatment modality was first introduced in the 1960s. Since this disease usually involves one or more limited joints, to prevent systemic effects and complications, topical treatments such as intra-articular infusions are critical in the treatment of the sickness ailment.¹⁶

In OA, a decrease in the concentration and molecular weight of endogenous hyaluronic acid (HA) alters the properties of synovial fluid, leading to damage to articular cartilage and worsening of symptoms.¹³ Exogenous HA treatment plays a role in maintaining the elasticity and viscosity of the synovial fluid and may reduce pain and improve function. In addition to this mechanical action, the role of HA as a mediator against inflammatory factors has been shown in various studies.¹⁶

Considering the high prevalence of KO and subsequent debilitating pain, it is necessary to investigate new therapeutic methods in this disease in order to improve the therapeutic methods and reduce the financial burden on the health system of the country. Therefore, the purpose of this study was to examine the impact of the intra-articular infusion of HA compounds on the gait pattern of patients with KO.

Methods

In this experimental study performed in 2013 at Imam Reza (501 Army) Hospital in Tehran, Iran, 43 patients with KO treated with intra-articular hyaluronic acid (IAHA) were studied. Sample size was determined based on sample size formula.

Inclusion criteria included patients aged 50-80 years with moderate KO (grade II or III based on Kellgren and Lawrence knee radiographic classification), having articular

fluid, no inflammatory rheumatologic disease including rheumatoid arthritis (RA), non-use of systemic or injectable corticosteroids two weeks before treatment and during treatment, and being unresponsive to conservative drug therapies and physiotherapy over the past 6 months.

Exclusion criteria included lack of major diseases such as pulmonary disease, renal failure, neoplasms, inflammatory arthritis, no history of knee surgery, history of intra-articular injection over the past 6 months, skin infection near the injection site, and general contraindications for intra-articular injection.

The present study was ethically approved by the Ethics Committee of AJA University of Medical Sciences, Tehran, Iran. Patients with OA referring to the Physical Medicine and Rehabilitation Clinic of Imam Reza Hospital who were qualified for incorporation in the study were assessed in 2013. All patients were examined and evaluated. Necessary imaging studies were performed including simple radiography. Finally, those who did not meet the exclusion criteria were included in the study.

Data were collected through a questionnaire, gait analysis, and goniometer. After obtaining informed consent from patients with inclusion criteria, the demographic questionnaire and Knee Injury and Osteoarthritis Outcome Score (KOOS) were completed by the patient. The knee ROM was measured using a goniometer and the gait pattern was assessed using the FDM Gait Analyzer (Zebris Co., Germany). Subsequently, IAHA (Hyaluron HEXAL manufactured by US Lifecore Biomedical Company) injection was performed three times in 15 days on a weekly basis. The KOOS was completed and knee ROM and gait pattern were re-evaluated 1 week, 1, 3, and 6 months after the last injection. This questionnaire has been validated and used as a standard tool to collect information on the QOL of patients with KO.

Data collected by the SPSS software (version 20, IBM Corporation, Armonk, NY,

USA) were normalized using the Kolmogorov-Smirnov statistical test (K-S test). Repeated measures analysis of variance (ANOVA) and paired t-test were used to analyze the changes. Mean and standard deviation (SD) were used to describe the quantitative variables and the number and percentage were used to describe the qualitative variables.

Results

Of 46 participants, 35 were women and 11 were men. Two subjects were excluded because of reluctance to cooperate in the project and one because of RA. The mean \pm SD of participants' age was 60.47 ± 7.83 years and the mean body mass index (BMI) of participants was 30.54 ± 53.4 kg/m² (Table 1).

Table 1. Demographic information of the participants

Variable	Mean \pm SD	Maximum	Minimum
Age (year)	60.47 ± 7.83	71.00	44.00
BMI (kg/m ²)	30.54 ± 4.53	39.06	19.49
Weight (kg)	80.14 ± 15.09	107.00	55.00
Height (cm)	161.77 ± 9.72	180.00	145.00

BMI: Body mass index; SD: Standard deviation

Stride length, stride time, cadence, and velocity were significantly different one week, 1, 3, and 6 months after the end of injection compared to pre-injection (Figure 1, A-D).

Other gait parameters including pressure changes, first metatarsophalangeal (MTP1), MTP2, heel, single support time, double support time, stance and swing phases, and changes in foot rotation one week, 1, 3, and 6 months after the end of injection compared to pre-injection were not statistically significant ($P > 0.05$) (Table 2).

The KOOS questionnaire data showed statistically significant changes in QOL one week, 1, 3, and 6 months after the end of injection compared to pre-injection (Table 3).

Investigation of the QOL of patients with KO in this study showed a significant improvement in patients' QOL after HA injection compared to pre-injection. The improvement trend is also noticeable in the short and long term (Figures 2 E-H, 3, and 4).

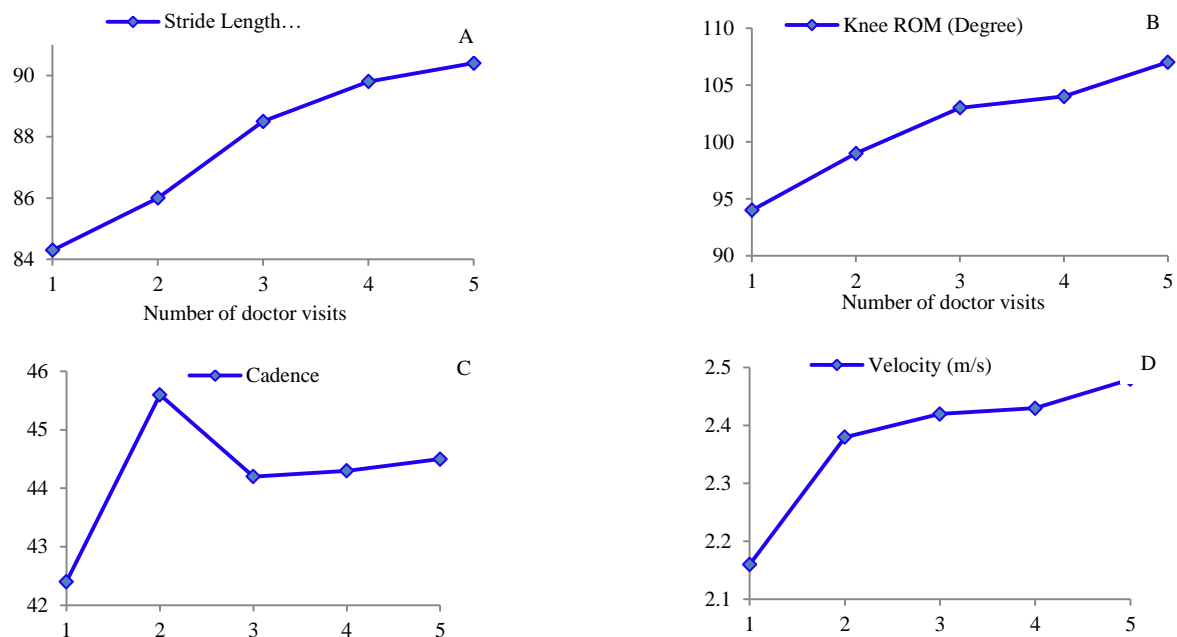


Figure 1. Comparison of changes in stride time, stride length, cadence, and velocity before injection (1), 1 week, 1, 3, and 6 months after injection (A-D)

Discussion

The results of this study showed that exogenous HA treatment increased the ROM of the knee joint. Increased knee ROM seems to be due to increased IAHA concentration and molecular weight resulting in altered synovial fluid properties and preservation of elasticity and viscosity of the synovial fluid. In addition,

the role of HA as a mediator acting against inflammatory factors has also been established, which reduces inflammation and knee swelling.¹⁶ Skwara et al. investigated the gait pattern in patients with KO after 5 sessions of weekly IAHA injection in Germany. Patients' pain was significantly reduced and their ROM increased after injection.¹⁷

Table 2. Investigation of gait parameters before and after intra-articular hyaluronic acid (IAHA) injection

Parameters	Visit 1 (before the intervention)	Visit 2 (1 week later)	Visit 3 (1 month later)	Visit 4 (3 months later)	Visit 5 (6 months later)	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
MTP1 pressure	17.3 ± 7.3	15.9 ± 6.9	17.7 ± 7.1	16.5 ± 6.8	15.2 ± 6.5	0.05
MTP2 pressure	20.2 ± 6.7	21.3 ± 7.5	20.7 ± 7.1	20.3 ± 7	19.7 ± 6.9	0.07
Heel pressure	19.5 ± 5.4	18.6 ± 6.0	18.7 ± 5.9	18.0 ± 5.6	18.0 ± 5.6	0.10
Stride length	84.5 ± 14.5	86.2 ± 14.4	88.8 ± 13.0	89.7 ± 13.1	90.7 ± 14.7	< 0.01*
Stride time	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.1	1.3 ± 0.2	3.1 ± 0.1	< 0.01*
Single support time	31.4 ± 3.4	31.6 ± 3.3	31.0 ± 3.0	31.8 ± 2.7	31.2 ± 3.1	0.30
Double support time	36.9 ± 5.3	37.1 ± 5.9	37.3 ± 6.8	37.8 ± 4.1	37.8 ± 6.1	0.50
Cadence	42.5 ± 6.1	45.5 ± 7.1	44.3 ± 6.2	44.5 ± 5.8	44.7 ± 7.2	< 0.01*
Velocity	2.2 ± 0.5	2.4 ± 0.7	2.4 ± 0.5	2.4 ± 0.5	2.5 ± 0.6	< 0.01*
Stance	68.6 ± 3.3	69.0 ± 3.4	69.4 ± 4.2	69.8 ± 3.5	69.9 ± 3.6	0.08
Foot rotation	12.5 ± 5.7	12.9 ± 5.6	12.9 ± 5.7	12.6 ± 5.2	12.3 ± 5.3	0.40

* P < 0.05

MTP1: First metatarsophalangeal; SD: Standard deviation

Table 3. Quality of life (QOL) assessment of patients with knee osteoarthritis (KO) before and 4 times after intra-articular hyaluronic acid (IAHA) injection

Parameters	Visit 1 (before the intervention)	Visit 2 (1 week later)	Visit 3 (1 month later)	Visit 4 (3 months later)	Visit 5 (6 months later)	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Symptoms	15.8 ± 15.0	57 ± 12.9	57.8 ± 8.7	61.7 ± 9.2	61.0 ± 11.4	< 0.01*
Stiffness	41.8 ± 16.3	61.1 ± 20.5	57.7 ± 21.5	63.6 ± 21.0	63.8 ± 21.9	< 0.01*
Pain	53.0 ± 12.8	64.0 ± 20.6	61.1 ± 21.0	67.3 ± 16.3	71.0 ± 15.1	< 0.01*
Function	27.9 ± 21.3	34.4 ± 29.8	33.7 ± 28.5	41.0 ± 28.8	60.6 ± 11.4	0.05
Sport activity	32.7 ± 23.8	28.6 ± 15.6	29.4 ± 18.4	35.4 ± 19.4	37.9 ± 18.1	< 0.01*
Final score	41.4 ± 9.8	49.0 ± 16.5	47.9 ± 15.4	53.8 ± 14.9	58.7 ± 22.9	< 0.01*

* P < 0.05

SD: Standard deviation

Investigation of the QOL of patients with KO in this study showed a significant improvement in patients' QOL after HA injection compared to pre-injection time. The improvement trend is also noticeable in the short and long term. The KOOS questionnaire examines the patient's QOL in 5 domains. The results of statistical analysis showed that

symptoms, stiffness, pain, function, and daily activity domains improved significantly after HA injection compared to the pre-injection time. Huang et al. showed that 5 IAHA injections were well tolerated and resulted in reduced pain and improved function in Asian patients with KO,¹⁸ which is consistent with the results of the present study.

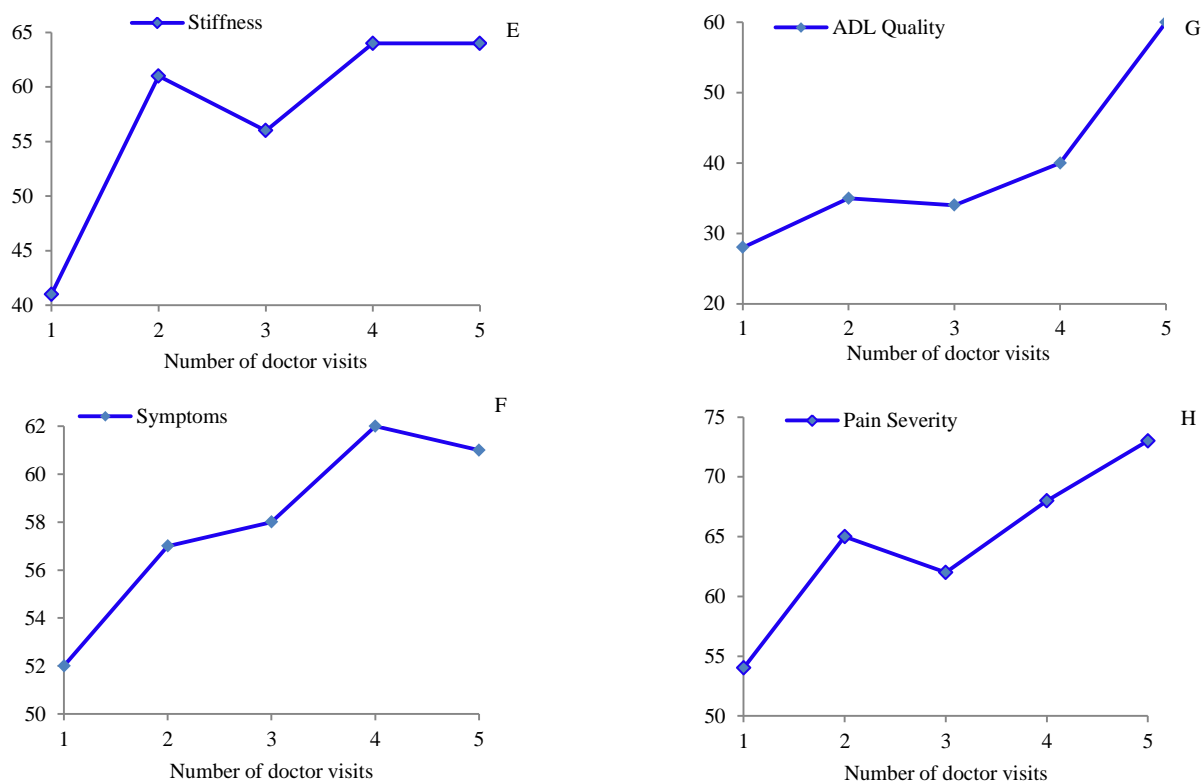


Figure 2. Evaluation of symptoms, stiffness, pain intensity, and quality of daily performance in patients with knee osteoarthritis (KO) before and 4 times after intra-articular hyaluronic acid (IAHA) injection (E-H)

Table 4. Investigation of knee joint range of motion (ROM) before and 4 times after intra-articular hyaluronic acid (IAHA) injection

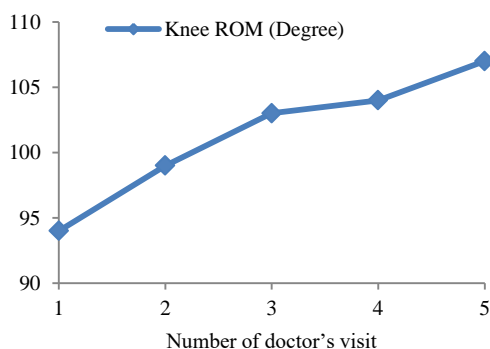
Parameters	Visit 1 (before the intervention)	Visit 2 (1 week later)	Visit 3 (1 month later)	Visit 4 (3 months later)	Visit 5 (6 months later)	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
ROM	93.9 ± 19.6	99.3 ± 19.8	103.0 ± 18.7	104.4 ± 20.4	107.0 ± 19.4	< 0.05*

* P < 0.05

ROM: Range of motion; SD: Standard deviation

**Figure 3.** Evaluation of the final changes in the quality of life (QOL) in patients with knee osteoarthritis (KO) before injection (1), 1 week, 1, 3, and 6 months after injection

Dieppe and Lim in a study in Italy, injected intra-articular sodium HA to 40 knees 3 times a week and showed a significant improvement in the intensity of spontaneous pain and pain following contact under load and during walking 3-8 weeks after the last injection. They also showed significant improvement in pain, stiffness, and function of patients after HA injection.¹¹ In another study, Lester and Zhang in Colombia examined the effect of IAHA on pain, QOL, and gait parameters of 53 patients with KO and found a significant decrease in the pain intensity.¹⁹

**Figure 4.** Examination of knee joint range of motion (ROM) before and 4 times after intra-articular hyaluronic acid (IAHA) injection

The results of the present study showed that stride length increased and stride time decreased after HA injection as compared to the pre-injection time. On the other hand, velocity and cadence increased. Considering the mechanism of action and properties of HA mentioned earlier, according to the consequences of this study, increasing knee ROM¹⁴ and decreasing pain during walking is expected to lead to increased stride length and decreased stride time leading to improved velocity and cadence, which is directly related to the step length and inversely related to the step time. Tang et al. observed changes in gait one week, 3, and 6 months after IAHA injection in 50 patients with OA in Taiwan. The results showed that the gait parameters, including velocity, cadence, stride time, and step length were significantly improved for at least 6 months after injection,²⁰ which is consistent with the results of the present study.

Smiderle et al. measured gait parameters after three IAHA injections in 40 patients with one-week intervals between the injections. Results showed that velocity and cadence, among all studied variables, improved significantly.²¹

However, Skwara et al.,¹⁷ unlike the present study, showed that these parameters did not change significantly. They attributed the insignificant changes in these parameters to the inadequate accuracy and sensitivity of the devices used during gait analysis. In a study on the effect of IAHA on gait, Dieppe and Lim also found a statistically insignificant increase in gait velocity.¹¹

The results of the present study revealed no statistically significant changes in the parameters of foot pressure distribution

(MTP1, MTP2, heel pressure), as well as swing and stance phases, single support time, double support time, and foot rotation, indicating no significant change in most objective parameters during the gait analysis after HA injection, although expected, which may be due to the complexity of the gait mechanism.

Conclusion

Intra-articular infusion of HA by increasing the elasticity and viscosity of the fluid in the

joint leads to pain reduction and improvement in gait parameters and QOL in patients with KO.

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Conflict of Interest

Authors have no conflict of interest.

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