Intra-articular hyaluronic acid injection vs. atorvastatin; which treatment is more effective in controlling symptoms of knee osteoarthritis? A clinical trial.

Jokar MH[1], Mirfeizi Z[2], Zarei H[3], Hashemzadeh K[2]

ACTA REUMATOL PORT. 2020;45:111-115

ABSTRACT

Background: Knee osteoarthritis is a disease of the elderly population. Two of the widely used treatment options for knee osteoarthritis is administration of oral atorvastatin and intra articular hyaluronic acid. This study was designed to compare the effects of oral atorvastatin and intra articular Hyaluronic acid in patients with knee osteoarthritis.

Method: This study was conducted under the approval of Mashhad University of medical sciences ethic committee. Seventy patients with knee OA were divided randomly into two groups; thirty-five subjects were given intra articular Hyaluronic acid injections weekly for three weeks and 35 were given atorvastatin 40 milligrams orally daily for 6 months. The WOMAC questionnaire was filled for each patient at the beginning of the study and every month up to 6 months. Data were analyzed with SPSS version 16.

Results: Enrolled subjects consisted of 28 males (40%) and 42 females (60%), and their mean age was 57.9±1.1 years. Study groups were similar regarding gender and age distribution (P=0.626, P=0.710, respectively). According to WOMAC questionnaire, pain score in the second month after injection was significantly lower in the Hyaluronic acid group compared with atorvastatin (P<0.001). Function score in the second month after injection was significantly lower in the Hyaluronic acid group compared with atorvastatin (P<0.001). These differences were absent in the following months.

Conclusion: Compared to atorvastatin group, significant improvements in pain symptoms and physical function of knee OA patients were observed in intra articular Hyaluronic acid treatment group in the second month after treatment. But this improvement did not last through the following months.

Keywords: Knee osteoarthritis; Hyaluronic acid; Atorvastatin.

1. Department of internal medicine, Emam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
2. Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3. Department of internal medicine, Shiraz University of Medical Sciences, Shiraz, Iran

INTRODUCTION

The most common cause of disability among adults is osteoarthritis (OA), with a lifetime risk of 44.7% in at least one knee, thus it puts a large socioeconomic burden on the society[1-3]. The most prevalent site of OA is the knees[4]. OA is believed to be caused by an imbalance of inflammatory and anti-inflammatory cytokines, resulting in the abnormal production of proteolytic enzymes in the joint space and thus the destruction of articular cartilage, subchondral bone, synovium, ligaments, and probably even the sensory nervous system[5]. Recommended available treatment options mostly target the patients' symptoms rather than affecting the biochemical characteristics of the joint[3,6]. Widely used medical and nonmedical managements of OA are as follows: educating the patients to exercise and lose weight, surgery, treatment with NSAIDs, acetaminophen or atorvastatin, or intra-articular injections of hyaluronic acid or corticosteroids[3,6,7].

Among the above mentioned treatment options, intra-articular (IA) injection of hyaluronic acid (HA) or corticosteroids have been used as an alternative or an adjacent therapy during the past 20 years[6]. HA is a long-chain polymer with repeating disaccharide units, with lubrication and elastic shock absorption characteristics[8]. The ability of the IA HA in delaying the need of total knee arthroplasty by up to 2 years has been shown by former

studies[6]. It acts by increasing synovial fluid, reducing stiffness, improving function and protecting the knee joints[3,8]. Being more advantageous over IA corticosteroids, HA has a longer effect on patients' symptoms and can be administered for long term OA treatment[9].

Oral statin intake is another long-term treatment plan which might be able to change the course of the disease[5,10]. Statins have been shown to effectively reduce inflammation in both animal and human studies[11]. In rabbits, atorvastatin inhibited the increase of IL-1 , TNF-α, and IL-6, while increasing IL-10, an anti-inflammatory cytokine. In human studies, atorvastatin was found to be a disease modifying antirheumatic drug (DMARD), which shows the effectiveness of therapy to reduce inflammation. Statins can alter the course of OA by at least two mechanisms: being an anti-inflammatory agent and lowering blood cholesterol[10]. There are reports stating hypercholesterolemia as an independent risk factor for the development of OA[12]. In addition, high levels of cholesterol are believed to leave negative structural changes even in asymptomatic people[2].

The two aforementioned managements have been used in the treatment of OA, however, no studies to date compare and discuss the efficacy of these treatments. Since the proper management of knee OA can improve patients' pain and functionality and potentially reduce the need for total knee arthroplasty, the current investigation was designed to assess the effectiveness of IA HA and oral atorvastatin treatments and to analyze their differences in improving patients' pain and functionality.

METHODS AND SUBJECTS

In this clinical trial, we enrolled 70 osteoarthritis (OA) patients from the rheumatology clinic of the Imam Reza Hospital, affiliated to Mashhad University of Medical Sciences. The inclusion criteria were: OA diagnosis based on American College of Rheumatology (ACR) criteria, being between 50-70 years old, and having a pain score of at least 60 measured from 0-100 millimeter visual analog scale (VAS). Subjects were educated about the study both verbally and by written information, and they were given time to ask any questions they had about the study. Patients were reassured they had the permission to leave the study at any point as they wish. All patients gave informed written consent to be recruited for the investigation. The investigation received the approval of Mashhad University of Medical Sciences Ethics Committee. The exclusion criteria were: secondary OA, systemic conditions (i.e. Diabetes), inflammatory joint disease (i.e. Rheumatoid arthritis), significant axial deviation (defined as varus or valgus of more than 50 degrees), coagulopathies, severe cardiovascular disorders, infections, immune disorders, patients treated with anticoagulants, and patients with hemoglobin levels of less than 11 milligrams per deciliter and platelet count of less than 150,000 per microliter. Initially, seventy patients were enrolled in the investigation and were randomized into two groups; a group receiving statin treatment and the other group receiving intra-articular hyaluronic acid (IAHA) injections (each group consisted of 35 patients). The statin group was treated with 40 milligrams of atorvastatin daily for 5 months. The IA HA group was given IA HA injections weekly for three weeks. We used Persian WOMAC questionnaire for pain measurements throughout the study (1). Subjects were asked to report their pain before the start of the study(baseline), and monthly for 5 months. It should be noted that patients were not prohibited from taking paracetamol or NSAIDs during the study except for 48 hours before each pain measurement.

The SPSS software version 16 (Statistical Package for Social Sciences, IBM, Chicago, Illinois, USA) was used for statistical analysis with descriptive statistics (mean, median, interquartile range, and standard deviation) being calculated for each variable. Kolmogorov-Smirnov test was used to check data for normality. To compare pairs of associated samples and pairs of independent samples, paired t-tests, and independent t-tests were applied. In all tests, P-value of ≤ 0.05 was defined to be statistically significant.

RESULTS

All 70 patients who were originally recruited completed the study. The patents were enrolled in the study, regardless of their occupation. Subjects were divided into two groups of 35 patients to compare the effectiveness of oral statin and intra-articular (IA) hyaluronic acid (HA) injection. The subjects in the statin group and IA HA group were of similar age and gender ($P > 0.05$). Baseline demographic information about the enrolled subjects are described in Table I.

In the atorvastatin intervention group, we observed that scores of pain, function, joint stiffness and the

TABLE I. COMPARISON OF DEMOGRAPHIC CHARACTERISTICS OF STUDY GROUPS

	IA HA	Atorvastatin	P-Value
Age	57.1 ± 4.4	58.6 ± 4.5	0.710
Gender (male)	15 (42%)	13 (37%)	0.626

IA HA: intra-articular hyaluronic acid. Values are expressed as means ± standard deviation or number (percent). Repeated measurement test and analysis of variance.

WOMAC score did not improve notably during the intervention (Table I).

In the IA HA intervention group, we found a statistically significant betterment in pain and function, and nearly significant improvement in WOMAC scores of patients in the first-month evaluation compared to the rest of the study. Almost all of the scores were better in the IA HA group compared to atorvastatin group, but none were of statistical significance except measurements of the first month (pain, function and WOMAC score, P<0.001, P<0.001 and P=0.056, respectively) (Table II).

Repeated measure analysis showed that age, gender and time had no significant effect on patients' pain and function during the study ($p > 0.05$). Repeated measure results only noted that pain and function were significantly better in the IA HA treatment group in the first month compared to other monthly scores ($p < 0.001$).

DISCUSSION

We found out that the function of the cases receiving intra-articular hyaluronic acid (IA HA) was significantly better than the atorvastatin group during the first month of the study. However, IA HA and atorvastatin had similar effects on pain and function of patients suffering from knee osteoarthritis (OA). OA is the most common joint disease of the population, especially amongst the elderly. The prevalence of osteoarthritis is increasing at a great pace.

Previous studies showed the effectiveness of IA HA and statin therapy for improving symptoms of OA. There are studies suggesting that these managements could even alter the course of the disease and delay its progression[2]. Regarding IA HA, it has been suggested that it improves knee joint function by a number of mechanisms, including improving biomechanical characteristics of synovial fluid such as viscoelasticity and lubrication of synovial fluid, suppressing gene expression in inflammatory mediators in the synovium that induced the production of endogenous HA; and modulation of gene expression of Africans and collagenase enzymes prevents cartilage degeneration[8,13]. Studies suggest it can improve muscle function and decrease co-contraction of the muscles for up to 6 months in patients who received neither analgesics nor physiotherapy[14,15]. In a study done by Skwara *et al.* they found out that the improvement of muscle coordination is not a short-term effect of the therapy compared with its effect on improving pain and knee function[9]. IA HA

TABLE II. COMPARISON OF PAIN, FUNCTION, JOINT STIFFNESS WOMAC AND TOTAL WOMAC SCORES AT DIFFERENT TIME POINTS

	WOMAC Pain		WOMAC Function		WOMAC Joint Stiffness		Total WOMAC	
	IA HA	Statin	IAHA	statin	IA HA	Statin	IA HA	statin
Baseline	39.2 ± 7	41.3 ± 6	135 ± 11	131 ± 13	16.5 ± 2	15.2 ± 9.6	190 ± 13	188 ± 15
1st month	28 ± 6	41.0 ± 4α	142.8 ± 8	133 ± 13α	16.8 ± 2	15.2 ± 7.8	194 ± 14	188 ± 14
2nd month	37.6 ± 8	40.0 ± 6	134 ± 9	132 ± 12	15.2 ± 4.6	15.2 ± 2.6	191 ± 10	188 ± 14
3rd month	37.6 ± 6	40.0 ± 6	135 ± 9	132 ± 18	15.2 ± 3.8	15.2 ± 2.6	192 ± 10	187 ± 22
4th month	39 ± 6	39.0 ± 6	133 ± 9	131 ± 19	15.2 ± 4.8	15.2 ± 1.7	191 ± 9	186 ± 24
5th month	38 ± 6	37.0 ± 7	134 ± 9	132 ± 19	15.2 ± 4.7	14.2 ± 9.8	187 ± 9	185 ± 25

IA HA: intra-articular hyaluronic acid; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. Values are expressed as mean ± standard deviation. α means significant difference in comparison with the IA HA group. Repeated measurement test and analysis of variance.

could potentially alter disease course as its effects are reported to be lasting longer than the drug's half-life[16]. In this study, we found out that IA HA could significantly improve pain, WOMAC score, and function during the first two months after the injections.

Regarding statin use, there is a large body of evidence showing the effectiveness of the treatment in animal models, however, there are not as many studies which were carried out on patients[5,7,17,18]. In vivo and in vitro studies illustrated that intra-articular injection of statins could reduce OA progression by several mechanisms, the most important of which are lipid metabolic effects and anti-inflammation effects[2,11,12]. It has been shown that studies exert their effect through monocyte or endothelial cell NF-kB activation inhibition[2]. Also, statins can protect against macroscopic and histopathologic cartilage damage through reducing matrix metalloproteinases by inhibiting IL-1b, and induce chondrocytes to synthesize aggrecan, bone morphogenetic protein 2, aggrecan, type 2 collagen and cartilage matrix proteoglycan. Statins also affect the differentiation of chondrocytes[2,5,19]. Han *et al.* showed ERK-1/2 and p38 kinase control the simvastatin-induced differentiation of chondrocytes in a way contending the OA progression in rabbits[20]. In addition to their anti-inflammatory effects, statins effects on lipid metabolism may also help in OA[12,18]. Previous observational research showed that high plasma cholesterol has an independent association with higher OA risk and that hypercholesterolemia can have destructive effects on the structure of joints even in asymptomatic patients[12]. On the contrary, Gierman *et al.* compared the effects of atorvastatin with ezetimibe, which has similar effects on plasma cholesterol, showing that atorvastatin was more effective in improving OA in mice[18]. This suggests that although cholesterol plays a role in the progression of OA, there are other processes involved in the development of OA. Their finding corroborates the above mentioned findings regarding the role of anti-inflammatory effects of statins.

Although there is a plethora of studies reporting on the effectiveness of statins in animal studies, clinical trials have reported controversial findings[5,7,17,18,21]. In a longitudinal study, Kadam *et al.* reported that using high dose and larger statin dose increments could decrease could reduce outcomes of clinically defined OA in patients who have been receiving statins for two years[10]. On the other hand, Michaelsson *et al.* reported there is no association between statin use and decreased consultations and surgery for OA[21]. In another study, Eymard *et al.* found out that using statins is associated with radiological worsening of knee OA in a three-year period, regardless of other confounding factors[22]. These reports were in line with our findings; in our study, we found that statin use did not significantly improve the WOMAC score and the sensation of pain in participants during 5 months of our study. The contrast between experimental animal studies and clinical trials might be due to several factors such as the duration of therapy, the way statins are administered, and dose adjusting for the drug to take their effect inside the human body. In our study, we found out that the improvements in function and pain of patients were significantly more pronounced in patients receiving IA HA compared with statins at the first month of the study. In addition, although not statistically different, the patients receiving IA HA experienced better functionality in the beginning month of the treatment. We also found out that the effectiveness of neither of the treatment options was associated with the duration of the treatment, sex, and age.

STRENGTH AND LIMITATIONS

Our study was conducted as a clinical trial, which makes it a valuable study regarding the evaluation of the effects of both treatment options in OA patients compared with studies experimenting on animal models. However, the study could be improved in a few ways. As an example, as reported in former studies, higher doses of statins could have a clinical improvement on OA; Effects of IA HA have been reported to depend on the baseline amount of HA in synovial fluid of the joint, thus we suggest that future studies try statins in higher doses, and evaluate patients who could benefit more from IA HA by evaluating them before recruiting them for their studies. By applying these measures in future studies, we hope the results could be of more practical value in addressing one of the most common illnesses that older populations are facing.

CONCLUSION

The positive effect of hyaluronic acid injections in function and pain of knee osteoarthritis patients after the first month of study has been illustrated in this study. However, this effect did not last through the following months. This indicates that while animal studies have

proven the effectiveness of IA HA and statin treatments, the results could not be applied to human studies and there are still larger human studies needed to prove the effectiveness of the treatments among the human population.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients gave informed written consent to be recruited for the investigation. The investigation received the approval of Mashhad University of Medical Sciences Ethics Committee (IR.MUMS.REC.1391.901).

CONSENT FOR PUBLICATION

All patients and healthy controls signed the consent for publication.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CORRESPONDENCE TO

Kamila Hashemzadeh
Department of Internal Medicine
Emam Reza Hospital, Mashhad University of Medical Sciences
Mashhad, Iran
E-mail: k.hashemzadeh@yahoo.com

REFERENCES

1. Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective. The American journal of nursing. 2012;112(3 Suppl 1):S13-19.
2. Wang Y, Tonkin A, Jones G, Hill C, Ding C, Wluka AE, et al. Does statin use have a disease modifying effect in symptomatic knee osteoarthritis? Study protocol for a randomised controlled trial. Trials. 2015;16:584.
3. Bhandari M, Bannuru RR, Babins EM, Martel-Pelletier J, Khan M, Raynauld JP, et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. Therapeutic advances in musculoskeletal disease. 2017;9(9):231-246.
4. Chang J, Liao Z, Lu M, Meng T, Han W, Ding C. Systemic and local adipose tissue in knee osteoarthritis. Osteoarthritis and cartilage. 2018.
5. Farnaghi S, Prasadam I, Cai G, Friis T, Du Z, Crawford R, et al. Protective effects of mitochondria-targeted antioxidants and statins on cholesterol-induced osteoarthritis. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2017;31(1):356-367.
6. Delbarre A, Amor B, Bardoulat I, Tetafort A, Pelletier-Fleury N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis - A Cox model analysis. PloS one. 2017;12(11):e0187227.
7. Goto N, Okazaki K, Akasaki Y, Ishihara K, Murakami K, Koyano K, et al. Single intra-articular injection of fluvastatin-PLGA microspheres reduces cartilage degradation in rabbits with experimental osteoarthritis. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2017;35(11):2465-2475.
8. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC musculoskeletal disorders. 2015;16:321.
9. Skwara A, Peterlein CD, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Changes of gait patterns and muscle activity after intraarticular treatment of patients with osteoarthritis of the knee: a prospective, randomised, doubleblind study. The Knee. 2009;16(6):466-472.
10. Kadam UT, Blagojevic M, Belcher J. Statin Use and Clinical Osteoarthritis in the General Population: A Longitudinal Study. Journal of General Internal Medicine. 2013;28(7):943-949.
11. Baker JF, Walsh P, Mulhall KJ. Statins: a potential role in the management of osteoarthritis? Joint, bone, spine : revue du rhumatisme. 2011;78(1):31-34.
12. Farnaghi S, Crawford R, Xiao Y, Prasadam I. Cholesterol metabolism in pathogenesis of osteoarthritis disease. International journal of rheumatic diseases. 2017;20(2):131-140.
13. Altman RD, Dasa V, Takeuchi J. Review of the Mechanism of Action for Supartz FX in Knee Osteoarthritis. Cartilage. 2018;9(1):11-20.
14. Tang AC, Hong WH, Chen HC, Tang SF. Intra-articular intervention by hyaluronic acid for knee osteoarthritis can modify locomotor pattern of muscle activity. Clinical neurology and neurosurgery. 2015;129 Suppl 1:S16-20.
15. Diracoglu D, Tuncay TB, Sahbaz T, Aksoy C. Single versus multiple dose hyaluronic acid: Comparison of the results. Journal of back and musculoskeletal rehabilitation. 2016;29(4):881-6.
16. Yudoh K, Karasawa R. Statin prevents chondrocyte aging and degeneration of articular cartilage in osteoarthritis (OA). Aging. 2010;2(12):990-998.
17. Bayyurt S, Kucukalp A, Bilgen MS, Bilgen OF, Cavusoglu I, Yalcinkaya U. The chondroprotective effects of intraarticular application of statin in osteoarthritis: An experimental study. Indian journal of orthopaedics. 2015;49(6):665-671.
18. Gierman LM, Kuhnast S, Koudijs A, Pieterman EJ, Kloppenburg M, van Osch GJ, et al. Osteoarthritis development is induced by increased dietary cholesterol and can be inhibited by atorvastatin in APOE*3Leiden.CETP mice--a translational model for atherosclerosis. Annals of the rheumatic diseases. 2014;73(5):921-927.
19. Simopoulou T, Malizos KN, Poultsides L, Tsezou A. Protective effect of atorvastatin in cultured osteoarthritic chondrocytes. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2010;28(1):110-115.
20. Han Y, Kim SJ. Simvastatin induces differentiation of rabbit articular chondrocytes via the ERK-1/2 and p38 kinase pathways. Experimental cell research. 2016;346(2):198-205.
21. Michaelsson K, Lohmander LS, Turkiewicz A, Wolk A, Nilsson P, Englund M. Association between statin use and consultation or surgery for osteoarthritis of the hip or knee: a pooled analysis of four cohort studies. Osteoarthritis and cartilage. 2017;25(11):1804-1813.
22. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyere O, et al. Statin use and knee osteoarthritis progression: Results from a post-hoc analysis of the SEKOIA trial. Joint, bone, spine : revue du rhumatisme. 2017.