

Evaluation of Effectiveness of Combined Intra-Articular Injection of Ozone and High Molecular Weight Hyaluronic Acid in Patients With Knee Osteoarthritis

Shervin Shahinpour¹, Mohsen Amirsabotki¹, Nader Ali Nazemian Yazdi^{1,2}

¹ Department of Anesthesiology and Pain Medicine, Amir A'lam Hospital, Tehran University of Medical Sciences, Tehran, Iran

² Pain Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Received: 14 Apr. 2023; Accepted: 21 Aug. 2023

Abstract- Osteoarthritis is one of the major causes of disability and a source of social cost in the elderly. Its prevalence is increasing due to ageing and increasing obese population. The knee is one of the most common joints to be affected by osteoarthritis and it can lead to serious effects on one's mobility, quality of life and livelihood. One of non-surgical treatments is intra-articular injection. Injection of both ozone and hyaluronic acid into knee joint are common methods for treatment of knee osteoarthritis. The aim of this study was to evaluate reduction of pain and improvement of function in patients who received combination of intra-articular injection of high molecular weight hyaluronic acid and ozone. In this retrospective case series study data of patients with knee osteoarthritis who underwent intra-articular injection of high molecular weight hyaluronic acid with ozone were evaluated. Participants had fulfilled Western Ontario and McMaster Universities Arthritis Index (WOMAC) short form questionnaire before, three days, one month and six months after the intra-articular injection. Pain reduction and function improvement factors were assessed according to the WOMAC short form questionnaire. A total of 65 patients were evaluated in this study. There was significant decrease in the total score of WOMAC SF (stiffness and function) in all three follow-ups ($P < 0.001$). Also, patients who had more severe pain before the injection benefited more from the intra-articular injection. Our study showed that the effectiveness of intra-articular injection of high molecular weight hyaluronic acid with ozone does not depend on the age, sex and BMI of patients. Injection of high molecular weight hyaluronic acid and ozone into the joint cause to significant improvement in patient's knee pain and function. It is recommended that the combination of high molecular weight hyaluronic acid and ozone be considered as an effective treatment in the process of these patients.

© 2023 Tehran University of Medical Sciences. All rights reserved.

Acta Med Iran 2023;61(9):567-571.

Keywords: Pain; High molecular weight hyaluronic acid; Osteoarthritis; Intra-articular injection; Ozone

Introduction

Osteoarthritis is the most common chronic joint disease, and its prevalence is increasing due to the increase in the average age of the population and the tendency to obesity (1,2). Osteoarthritis causes significant economic, social and psychological costs. According to the reports osteoarthritis is a major cause of global overhead economic burden in all countries (3,4). Osteoarthritis of the knee is the most common type, and according to the studies conducted, its prevalence in Iran is about 34% in people over 15 years of age (5,6).

Osteoarthritis causes significant morbidity due to disability caused by pain and clinical complaints and limitation of joint range of motion (7,8).

In osteoarthritis, the cartilage of the knee joint is destroyed, with the destruction of the cartilage, the protective layer between the two bones decreases and causes pain during movement (9).

Although surgery relieves the pain caused by knee arthritis and allows the patient to return to previous activities, not all patients are suitable candidates for anesthesia and surgery so alternative treatments have become important. These treatments include lifestyle

Corresponding Author: N.A. Nazemian Yazdi

Department of Anesthesiology and Pain Medicine, Amir A'lam Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166703819, E-mail address: drmnazemian@gmail.com

Copyright © 2023 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited

Knee injection of ozone and high molecular weight hyaluronic acid

changes, systemic drug use (such as anti-inflammatory drugs) and intra-articular injection of corticosteroids or hyaluronic acid (10).

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been recognized for a long time as the main treatment for mild to moderate osteoarthritis, but they are not tolerated by all patients due to side effects (11,12).

Intra-articular injection of corticosteroids has been reported to be effective and well tolerated, but should be limited to 3-4 injections per year, as they reduce the function of sensory receptors and progressive destruction of articular cartilage and cause Charcot joint (13). One of the appropriate solutions for patients who do not respond to conventional conservative treatments or experienced severe side effects is intra-articular injection of hyaluronic acid alone or ozone alone (14,15).

Ozone gas is available in a mixture of oxygen and ozone (16,17).

It improves tissue oxygenation and has anti-inflammatory and analgesic effects (15,18-22) but due to increased risk of some complications such as pain or septic arthritis in any invasive articular procedure the number of injections should be minimal (23).

One of the new treatments is simultaneous intra-articular injection of hyaluronic acid and ozone, which has better results than using each one alone. The purpose of this study is to evaluate the pain reduction and functional improvement in patients with knee osteoarthritis who had intra-articular injection of high molecular weight hyaluronic acid (HMW HA) with ozone.

The present study was designed to evaluate the efficacy of HMW HA, and ozone administered simultaneously by injection in patients with OA of the knee.

Materials and Methods

In this retrospective case series study, data of patients who visited the pain clinic of Amir Alam Hospital from May 2020 to June 2021 and were candidates for intra-articular injection of high molecular weight hyaluronic acid with ozone were reviewed. The study was approved by the Ethics committee of the Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.726) and followed the Helsinki declaration principles patients willing to participate in the study signed informed consent.

Inclusion criteria

1. Patients between the ages of 20 and 80, male and

female, with grade II and III knee osteoarthritis referred to the pain clinic of Amir Alam Hospital from 2020 to 2021.

2. Failure to respond to usual conservative treatments, including painkillers and NSAIDs, or the inability to continue usual conservative treatments.

We screened data of 65 patients with grade II and III knee osteoarthritis who visited the pain clinic of Amir Alam Hospital from May 2020 to June 2021 and underwent intra-articular injection of high molecular weight hyaluronic acid with ozone.

Patients were visited, examined and fulfilled WOMAC short form questionnaire before intra-articular injection, three days, one month and six months after injection.

Intra-articular injection of patients was performed under C-Arm guide with Viscor gel which contains sodium hyaluronate 2% with high molecular weight (50 mg, 2.5 ml) that requires only one injection. At the same time, 10cc of ozone with a concentration of 30mcg was injected for the patients.

The exclusion criteria were patient refusal, performing any new intervention on the affected knee during the study period, history of performing any intervention on the affected knee, unusual decrease or increase in physical activity in study period.

All analyses were performed by SPSS software SPSS 20 (Statistical Package for Social Sciences) and Statistical significance was considered at $P < 0.05$.

Results

Demographic data and different WOMAC short form questionnaire of 65 patients (54 females and 11 males) were evaluated in this study.

The average age of the patients in this study was 62.63 ± 10.41 years. None of the patients experienced an allergic reaction, painful reaction, or septic arthritis after the injection.

Figure 1 shows the histogram of age distribution in patients.

WOMAC SF total score index before injection in patients was 33.6 ± 8.00 , which decreased to 14.21 ± 10.90 on the third day 11.35 ± 11.89 on the first month, and 15.01 ± 13.76 on the sixth month. The WOMAC SF total score decreased significantly in all three follow-ups ($P < 0.001$).

Table 1 and figure 2 show the improvement of the pain severity before the intervention and on the third day,

the first month and the six months after the injection.

We also found patients with more severe pain had

more pain reduction and function improvement after injection.

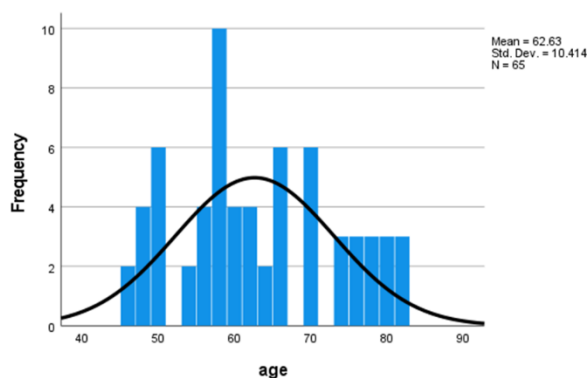


Figure 1. Histogram of age distribution in patients

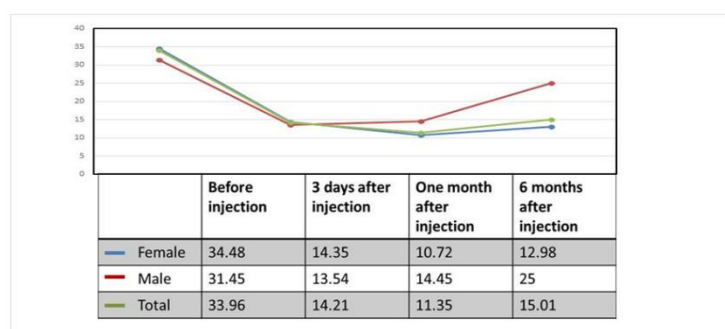


Figure 2. Evaluation of pain before and after injection

Table 1. WOMAC SF total score before and after intervention (third day, first month and the sixth months after)

WOMAC SF score	Mean	SD	P
Before injection	33.96	8.00	--
Three days after injection	14.21	10.90	<0.001
Before injection	33.96	8.00	--
One month after injection	11.35	11.89	<0.001
Before injection	33.96	8.00	--
Six months after injection	15.01	13.76	<0.001

For this purpose and according to the difference in severity of pain of each patient before the injection, a new variable called the amount of improvement in pain and function was created, which was the result of subtracting the WOMAC SF score after the injection from the WOMAC SF score before the injection. Then, using Pearson's correlation coefficient, the relationship between pain improvement and knee function was investigated with the pain severity before injection.

Neither age nor BMI of patients showed any

significant correlation with improvement in pain or function.

Discussion

The first studies about injection of hyaluronic acid in human knee osteoarthritis were performed by Rydell in 1970 and Peyron in 1974 (21,24).

Aviad and Houpt (25) suggested that the beneficial effect of injected HA might be due to pharmacological

rather than physical properties. Wobig *et al.*, (26) reported that HMW HA had a significantly greater pain-relieving effect than low molecular weight (LMW) HA. Also, it has been suggested that LMW HA is more chondroprotective but HMW HA have more anti-inflammatory properties (27).

In 1974, Peyron *et al.*, injected 1, 2, or 3 mL of hyaluronic acid (Hylon) for 23 patients and obtained a positive response in relation to pain and function in 74% of patients. Based on their results, it was proved that the treatment with two separate injections of 2 ml of hyaluronic acid has the best results in patients (24).

Our results in this study showed that intra-articular injection of hyaluronic acid with high molecular weight along with ozone significantly improves knee pain and function of patients both in the short term (three days and one month) and in the medium term (six months).

Hyaluronic acid not only relieves the symptoms of osteoarthritis, but also changes the structure of the patient's joint and the rate of progression of the osteoarthritis disease, at least early in the evolution of the disease process (28).

Based on the results of Ohkwaru *et al.*, intra-articular injection is an effective treatment for knee osteoarthritis with beneficial effects on pain and function of patients in different periods after injection. Hyaluronic acid injection shows its effect especially in 5 to 13 weeks after the injection with a significant effect in reducing the monthly consumption of NSAIDs.

Although adverse effects such as allergic reactions may be higher in HMW HA injection we believe that HMW HA injections would be associated with fewer total complications than LMW HA because less intra-articular injections are needed. On the other hand, recent studies demonstrated that lower or even single HMW HA has same clinical outcomes with LMW HA (29,30). Thus, it can be considered that recently presented HMW HA, Hyruan Plus® is relatively safe with less patient discomfort due to fewer injections needed.

In this study we had some limitations such as relatively small study population, also measurement of pain is usually subjective and the lack of precise tools to measure it.

Although in this study no adverse effects happened after injection further studies with larger study population is recommended.

Acknowledgements

The authors would like to thank the Research Development Center Amir Alam Hospital, and anesthesia

and surgical technicians of Hospital for their assistance.

References

1. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. *Indian J Med Res* 2013;138:185-93.
2. Sekar S, Crawford R, Xiao Y, Prasadam I. Dietary Fats and Osteoarthritis: Insights, Evidences, and New Horizons. *J Cell Biochem* 2017;118:453-63.
3. Chen A, Gupte C, Akhtar K, Smith P, Cobb J. The Global Economic Cost of Osteoarthritis: How the UK Compares. *Arthritis* 2012;2012:698709.
4. Salmon JH, Rat AC, Sellam J, Michel M, Eschard JP, Guillemin F, et al. Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies. *Osteoarthritis Cartilage* 2016;24:1500-8.
5. Hsieh RL, Lee WC. Effects of Intra-articular Coinjections of Hyaluronic Acid and Hypertonic Dextrose on Knee Osteoarthritis: A Prospective, Randomized, Double-Blind Trial. *Arch Phys Med Rehabil* 2022;103:1505-14.
6. Rezasoltani Z, Azizi S, Najafi S, Sanati E, Dadarkhah A, Abdorrazaghi F. Physical therapy, intra-articular dextrose prolotherapy, botulinum neurotoxin, and hyaluronic acid for knee osteoarthritis: randomized clinical trial. *Int J Rehabil Res* 2020;43:219-27.
7. Sharif M, George E, Shepstone L, Knudson W, Thonar EJ, Cushnaghan J, et al. Serum hyaluronic acid level as a predictor of disease progression in osteoarthritis of the knee. *Arthritis Rheum* 1995;38:760-7.
8. McDonough CM, Jette AM. The contribution of osteoarthritis to functional limitations and disability. *Clin Geriatr Med* 2010;26:387-99.
9. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84:351-8.
10. Ringdahl E, Pandit S. Treatment of knee osteoarthritis. *Am Fam Physician* 2011;83:1287-92.
11. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;43:593-9.
12. Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthritis Cartilage*. 2016;24:962-72.
13. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;2:CD005328.

14. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ* 2004;328:869.
15. Escobar A, Vrotsou K, Bilbao A, Quintana JM, Garcia Perez L, Herrera-Espineira C. Validation of a short form of the function dimension of the WOMAC questionnaire. *Gac Sanit* 2011;25:513-8.
16. Manoto SL, Maepa MJ, Motaung SK. Medical ozone therapy as a potential treatment modality for regeneration of damaged articular cartilage in osteoarthritis. *Saudi J Biol Sci* 2018;25:672-9.
17. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Arch Med Res* 2006;37:425-35.
18. Hawker G, Melfi C, Paul J, Green R, Bombardier C. Comparison of a generic (SF-36) and a disease specific (WOMAC) (Western Ontario and McMaster Universities Osteoarthritis Index) instrument in the measurement of outcomes after knee replacement surgery. *J Rheumatol* 1995;22:1193-6.
19. Yang KG, Raijmakers NJ, Verbout AJ, Dhert WJ, Saris DB. Validation of the short-form WOMAC function scale for the evaluation of osteoarthritis of the knee. *J Bone Joint Surg Br* 2007;89:50-6.
20. Nadrian H, Moghimi N, Nadrian E, Moradzadeh R, Bahmanpour K, Iranpour A, et al. Validity and reliability of the Persian versions of WOMAC Osteoarthritis Index and Lequesne Algofunctional Index. *Clin Rheumatol* 2012;31:1097-102.
21. Rydell N, Balazs EA. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. *Clin Orthop Relat Res* 1971;80:25-32.
22. Sconza C, Di Matteo B, Queirazza P, Dina A, Amenta R, Respizzi S, et al. Ozone Therapy versus Hyaluronic Acid Injections for Pain Relief in Patients with Knee Osteoarthritis: Preliminary Findings on Molecular and Clinical Outcomes from a Randomized Controlled Trial. *Int J Mol Sci* 2023;24:8788.
23. Frizziero L, Govoni E, Bacchini P. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: clinical and morphological study. *Clin Exp Rheumatol* 1998;16:441-9.
24. Peyron JG, Balazs EA. Preliminary clinical assessment of Na-hyaluronate injection into human arthritic joints. *Pathol Biol (Paris)* 1974;22:731-6.
25. Aviad AD, Houpt JB. The molecular weight of therapeutic hyaluronan (sodium hyaluronate): how significant is it? *J Rheumatol* 1994;21:297-301.
26. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther* 1999;21:1549-62.
27. Huang TL, Hsu HC, Yang KC, Yao CH, Lin FH. Effect of different molecular weight hyaluronans on osteoarthritis-related protein production in fibroblast-like synoviocytes from patients with tibia plateau fracture. *J Trauma* 2010;68:146-52.
28. Ohkawara Y, Tamura G, Iwasaki T, Tanaka A, Kikuchi T, Shirato K. Activation and transforming growth factor-beta production in eosinophils by hyaluronan. *Am J Respir Cell Mol Biol* 2000;23:444-51.
29. Bahrami MH, Raeissadat SA, Cheraghi M, Rahimi-Dehgolan S, Ebrahimpour A. Efficacy of single high-molecular-weight versus triple low-molecular-weight hyaluronic acid intra-articular injection among knee osteoarthritis patients. *BMC Musculoskelet Disord* 2020;21:550.
30. Lee PB, Kim YC, Lim YJ, Lee CJ, Sim WS, Ha CW, et al. Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial. *J Int Med Res* 2006;34:77-87.