

# The Comparison of the Effects of Intra-articular Ozone and Polynucleotide Gel Injections in Pain Management of Knee Osteoarthritis

## Diz Osteoartritinde Ağrı Yönetiminde İntra-artiküler Ozon ve Polinükleotid Jel Enjeksiyonlarının Karşılaştırılması

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### Abstract

Numerous treatment methods, ranging from non-pharmacologic to pharmacological approaches, are in existence for knee osteoarthritis. Injections of intra-articular ozone and polynucleotides (Condrotide) have become popular in the treatment. However, clinical value and cost-effectiveness of the treatment methods have not been completely determined. The aim of the study is to compare the efficacy of intra-articular ozone and polynucleotide gel injections in patients, who have knee pain, related to osteoarthritis in the process of 12-weeks. Data of the study were obtained between the dates of January 2018 and August 2018. Besides, the data of the patients were attained by being scanned retrospectively. The patients who were applied intra-articular ozone (n=30) or polynucleotides (n=32) in per routine protocol were selected and included. Four sessions of intra-articular ozone injection in patients who were in the first group were applied weekly and one session of polynucleotides gel was applied to the patients who were in the second group. Pain levels of patients were recorded at the baseline, 5 weeks after the treatment and 12 weeks post treatment by utilizing the Numeric Rating Scale. Significant improvements were seen in both groups in 5 weeks and 12 weeks posttreatment assessments compared to baseline (p<0.001). There was no significant difference between groups of 5 weeks (p=0.855) and 12-weeks (p=0.554) posttreatment. No adverse events were reported. Therefore, intra-articular ozone treatment may be considered as effective as polynucleotides injections for pain relief in patients with knee osteoarthritis. Based on the current evidence, more trials are needed for further scientific evidence.

**Keywords:** Injection, Intra-articular, Osteoarthritis, Ozone, Polynucleotides

### Öz

Diz osteoartriti tedavisinde farmakolojik ve farmakolojik olmayan birçok tedavi yöntemi mevcuttur. İntra-artiküler ozon ve polinükleotid jel (Condrotide) enjeksiyonları da son yıllarda diz osteoartriti tedavisinde popüler olmuştur. Buna rağmen bu tedavi yöntemlerinin klinik değeri ve maliyet-etkinlikleri tam olarak ortaya konmamıştır. Bu çalışmada osteoartrite bağlı diz ağrılı hastalarda intra-artiküler ozon ve polinükleotid jel enjeksiyonlarının 12 haftalık takip sürecinde etkinliklerini karşılaştırmak amaçlanmıştır. Çalışmanın verileri Ocak 2018 ve Ağustos 2018 tarihleri arasında diz osteoartritine bağlı diz ağrılı olan hastaların verileri retrospektif olarak taranarak elde edilmiştir. Çalışmaya diz bölgesine rutin bir protokole intra-artiküler ozon (n=30) veya polinükleotid jel (n=32) uygulanan hastalar dahil edilmiştir. Birinci gruptaki hastalara haftada bir olacak şekilde 4 seans intra-artiküler ozon enjeksiyonu; 2. gruptaki hastalar 1 seans polinükleotid jel uygulanmıştır. Hastaların ağrıya yönelik değerlendirmeleri tedavi öncesi, tedaviden 5 hafta sonra ve tedaviden 12 hafta sonra Numerik Ağrı Skalası kullanılarak yapılmıştır. Her iki grupta da tedavi öncesi ile kıyaslandığında 5. hafta ve 12. hafta değerlendirmelerinde anlamlı gelişme gözlenmiştir (p<0.001). Gruplar arasında 5. hafta (p=0.855) ve 12. hafta (p=0.554) değerlerinde istatistiksel olarak anlamlı fark gözlenmemiştir. Tedavi süreçlerinde beklenmeyen bir yan etki raporlanmamıştır. Bu nedenle, osteoartrite bağlı diz ağrısı olan hastalarda intra-artiküler ozon enjeksiyonu tedavisinin ağrıyı azaltmada en az polinükleotid jel enjeksiyonu kadar etkili olabileceği düşüncesindeyiz. Bu veriler ışığında daha ileri düzeyde bilimsel kanıt için daha fazla çalışmaya ihtiyaç vardır.

**Anahtar Kelimeler:** Enjeksiyon, İntraartiküler, Osteoartrit, Ozon, Polinükleotid

### Introduction

Knee osteoarthritis (OA) is the most common joint disease and is one of the major causes of disability in the elderly population. Increased dependence and pain in daily living activities such as walking, climbing stairs and balance lead to progressive loss of function and physical disability in patients with knee OA (1,2). Diagnosis of knee OA can be confirmed by medical history, clinical and radiological features. Diagnosis may also be possible according to the American College of

Rheumatology criteria published in 2010 (3). There is no curative treatment method in the management of knee OA, so the aim of current treatments is to reduce the pain and movement restriction and to maintain maximum independence of the patient in activities of daily living. Optimal management of knee OA requires a combination of therapies including non-pharmacological and pharmacological modalities. İntra-articular therapy is usually preferred for treatment of knee OA. This type of treatment is especially recommended in patients who did not respond to acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), or in patients who have contraindications for NSAIDs (4). Intra-articular ozone and polynucleotides injections became popular for the treatment of knee OA, despite the clinical value and cost-effectiveness not being definitely determined. The aim of this study is to compare the 12-weeks efficacy in pain relief of intra-articular injections of ozone and polynucleotides in patients with knee OA.

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## Material and Method

The current study is performed retrospectively. Medical records of 462 patients who were referred between January and August 2018 (add) with the complaint of knee pain due to OA were analyzed. A total of 62 patients with Stage 2 or 3 knee OA according to Kellgren-Lawrence Classification between the ages of 33-97, who had a single injection of intra-articular polynucleotide (n=32) or 4 sessions of intra-articular ozone within an interval of four weeks (n=30), were included in the study. Patients who received any analgesic therapy (including additional intra-articular injection) or physical therapy after the injection were excluded. Patients were divided two groups as group1 and group 2. Group 1: This group included patients who received 20 mcg/ml of intra-articular ozone injection in the first session, 15 mcg/ml in the second session, 10 mcg/ml in the third and fourth sessions each, as a total of 4 sessions in an interval of 1 week. 20 ml ozone is used in each application. Group 2: Patients who received 2 ml of intra-articular gel containing 20 mg/ml polynucleotide for one session were included in this group.

All applications were performed by the same physician. The same injection technique was used in all applications with anterolateral approach as the patient was in supine position and his/her knee flexion angle was 90 degree. All of the applications were performed under sterile conditions. The patients subject to study provided their detailed medical history related to their complaints to a certain physician in physiotherapy outpatient clinic before the applications of knee injections. The same physician examined them and evaluated their suitability for local ozone or polynucleotide gel injections. The patients who were deemed suitable for the injections and accepted the therapy with informed consent form were administered local ozone or polynucleotide gel injections.

Pain severity of patients measured by Numeric Rating Scale (NRS), and was recorded at baseline (T0), 5 weeks (T1) and 12 weeks (T2) post-treatment. All evaluations were performed by another physician.

The statistical evaluation of the data obtained in our study was done using "SPSS 22.0 Statistical Program". The Kolmogorov-Smirnov test was applied to determine whether the data were within normal distribution. Chi-Square test was used to compare categorical data between groups. Student t test and Mann Whitney-U test was used to compare nominal data between groups.

Friedman test was used to assess if there was statistically significant difference between the intergroup data at T0, T1, T2 evaluations. Post-hoc analysis was performed using the Wilcoxon test upon determination of a statistically significant change.

The statistical differences between the NRS scores of groups were evaluated by Mann-Whitney U test during the T0, T1 and T2 evaluations. In this study,  $p < 0.05$  was considered as significant.

## Results

There was no statistically significant difference between the groups in terms of age ( $p=0.996$ ) and gender ( $p=0.658$ ) of the patients in our study. No statistically significant difference was found between the two groups when pre-treatment NRS parameters were evaluated ( $p=0.934$ ) (Table 1).

**Table 1.** Demographic data and baseline NRS scores.

Demographic Data	Group 1 (n=30)	Group 2 (n=32)	P
Age, mean±SD (min-max)	64.73±14.85 (33-97)	64.71±11.02 (47-88)	0.996
Gender, M/F % (n)	77/23 (23/7)	81/19 (26/6)	0.658
NRS Score-T0, mean±SD (median) (min-max)	7.56±1.16 (8) (4-10)	7.53±1.04 (8) (5-9)	0.934

-Student t test was used for comparing means (age) between groups.  
 -Chi-square test was used for comparing categorical data (gender) between groups.  
 -Mann Whitney U test was used for comparing means (NRS scores) between groups.

Significant improvements were seen in both groups in 5-week and 12-week posttreatment compared to baseline ( $p < 0.001$  for all comparisons) (Table 2).

**Table 2.** Intragroup comparison of NRS parameters

	NRS score	
	Group 1 mean±SD (median) (min-max)	Group 2 mean±SD (median) (min-max)
<b>T0</b>	7.56±1.16 (8) (4-10)	7.53±1.04 (8) (5-9)
<b>T1</b>	4.06±1.41 (4) (1-7)	4.03±1.37 (4) (2-7)
<b>T2</b>	4.10±1.12 (4) (2-6)	4.00±1.21 (4) (1-7)
<b>p*</b>	<0.001	<0.001
<b>p#</b>	<0.001	<0.001

NRS: Numeric rating scale  
 \* p values for the comparison of NRS scores between T0 and T1 in group 1 and group 2  
 # p values for the comparison of NRS scores between T0 and T2 in group 1 and group 2  
 Friedman test and Wilcoxon test was used for intragroup comparisons

In addition, there was no significant difference between groups at baseline ( $p=0.934$ ), 5 weeks ( $p=0.855$ ) and 12-weeks ( $p=0.554$ ) post-treatment (Table 3). No adverse event was reported.

**Table 3.** Intergroup comparison of NRS parameters.

NRS	T0	T1	T2
Group 1			
mean±SD	7.56±1.16	4.06±1.41	4.10±1.12
(median)	(8)	(4)	(4)
(min-max)	(4-10)	(1-7)	(2-6)
Group 2			
mean±SD	7.53±1.04	4.03±1.37	4.00±1.21
(median)	(8)	(4)	(4)
(min-max)	(5-9)	(2-7)	(1-7)
p	0.934	0.855	0.554

Mann-Whitney U test was used intergroup comparison of NRS scores at T0, T1 and T2

## Discussion

Both ozone and polynucleotide injections were found to be effective in this study, which we aimed to compare the efficacy of intra-articular ozone and polynucleotide injections on pain in the 12-week follow-up period in patients with osteoarthritis-related knee pain.

Studies evaluating the efficacy of intra-articular ozone injection in patients with knee OA are limited in the literature (5,6,7,10). On the other hand, in the literature, we have not found any study comparing the efficacy of intra-articular polynucleotide injection with ozone injection.

Raeissadat SA et al. randomized 174 patients with knee OA into two groups, and applied intra-articular hyaluronic acid to one group and ozone to the other group (5). Hyaluronic acid and ozone injections were applied once a week, for a total of 3 sessions. 10 ml ozone gas at a dose of 30 mcg/ml was used in applications. Visual Analogue Scale (VAS) and The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) showed statistically significant improvement compared to the baseline values in both groups. There was also no statistically significant difference in side effects between the groups. In our study, ozone injection was administered once a week with a total of 4 sessions, at 20/15/10/10 mcg/ml doses and 20 ml volumes per session. Similar to the study of Raeissadat et al., our study also showed a statistically significant decrease in the NRS score of the patients at the 5th week, which continued until the 12th week.

Duymus TM et al. randomized 102 patients with Stage 2-3 symptomatic knee OA into three groups and compared the effectiveness of intra-articular PRP, hyaluronic acid and ozone injection (6). First group received a total of 2 PRP doses being once per month, second group received a single dose of hyaluronic acid and the third group received a total of 4 doses of ozone in a 15 ml volume at a dose of 30mcg/ml per week. They evaluated the efficacy of the treatment before and at 1st, 3rd, 6th and 12th months after treatment with VAS and WOMAC scores. The improvement in VAS and WOMAC scores were statistically significant in all patients at

1st month after treatment and no difference was found between the groups. Statistically significant improvement in VAS and WOMAC scores have been decreased in the patients who received ozone injection at the 3rd month after treatment, and at the 6th month they returned to pre-treatment values. Hyaluronic acid and PRP efficacy continued at the 6th month, but the statistically significant improvement which was achieved with only PRP at the end of 12 months continued. Similarly, in our study, the significant reduction in NRS scores at the 5th week after treatment continued until the 12th week, following both ozone and polynucleotide injections.

Giombini A et al. randomized 70 patients with symptomatic knee OA into three groups and applied intra-articular oxygen-ozone, hyaluronic acid and combination of both (7). Statistically significant improvement was observed in Knee Injury and Osteoarthritis Outcome Score (KOOS) and VAS scores after treatment in all three groups. However, they found the combination of ozone and hyaluronic acid superior to monotherapy. On the other hand, Giarratana LS et al. in their study, in which they aimed to compare the efficacy of intra-articular polynucleotide and hyaluronic acid, randomized 72 patients into two groups; Group 1 received three doses of polynucleotide once a week and Group 2 received three doses of hyaluronic acid (8). The increase in KOOS scores and the reduction in pain were statistically significant in all patients compared to baseline. However, in patients receiving polynucleotide, treatment efficacy started at the end of the 2nd week, whereas in patients who received hyaluronic acid, it started at 18th week. In our study, the positive effect obtained with both the intra-articular ozone and the polynucleotide started at the 5th week following injection and continued for at least 12 weeks.

One of the main goals of the treatment of knee OA is to control the knee pain of the patient as much as possible to promote independence through the patient's daily living activities and to improve their functionality. When polynucleotide gel is applied intra-articularly, it supports the physiological repair process by binding water molecules at high concentration, thus contributing to the restoration of articular microenvironment and restoration of chondrocyte homeostasis (9). Ozone reduces serum levels of inflammatory mediators by suppressing TNF- $\alpha$ . It accelerates the breakdown of free oxygen radicals by increasing the activity of superoxide dismutase, thus slowing the degenerative process. It also produces an analgesic and anti-inflammatory effect with the inhibition of phospholipase A2 (10).

In our study, we compared the intra-articular polynucleotide injection, which is one of the current treatment modalities, with intra-articular ozone injection in the treatment of knee pain due to osteoarthritis, and we suggest that it may be a

reliable, effective analgesic treatment option with low cost and extremely low side effect potential.

#### Limitations

In this study, the effects of intra-articular ozone and polynucleotide treatment on pain score in patients with knee osteoarthritis were evaluated. However, the possible effects on quality of life and functional limitation were not evaluated. In our study, since the patient follow-up was done until the end of the 12th week, it was not possible to comment on the effect of intra-articular ozone and polynucleotide injection lasting more than 12 weeks, on knee pain due to knee osteoarthritis.

In addition, there are problems to obtain ethics committee approval for prospective ozone related studies. Therefore, most of the studies are retrospective. The another limitation of the present study is that it is also retrospective study.

#### Conclusion

Both intra-articular ozone and polynucleotide injections appear to be effective for pain relief in patients with knee OA. An analgesic effect of up to 12 weeks can be obtained with 4 sessions of intra-articular ozone once a week or 1 session of polynucleotide treatment. In addition, intra-articular ozone therapy may be considered as effective as intra-articular polynucleotide injections for pain relief. At the same time, intra-articular ozone therapy can be preferred as a cost-effective treatment method in managing knee pain due to osteoarthritis and an alternative to oral analgesic/anti-inflammatory agents and other intra-articular medications. Based on the current evidence, more trials are needed for further scientific evidence.

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