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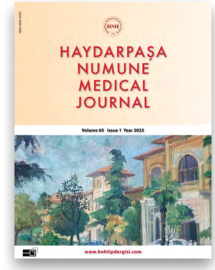

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ORIGINAL ARTICLE

The Effects of Intraarticular Ozone Injection on Pain, Functional Status and Activities of Daily Living in Patients with Knee Osteoarthritis

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Abstract

Introduction: Knee osteoarthritis (KOA) is a common painful joint disease. Although many pharmacological and non-pharmacological treatment methods are available, the use of traditional and complementary medicine approaches has increased in recent years. Intra-articular ozone injection is considered an effective and cost-effective method among these approaches and has been shown to be beneficial in painful musculoskeletal conditions in various studies. The aim of this study was to evaluate the short- and medium-term effects of intra-articular ozone injection on pain, functional status, and activities of daily living in patients with knee osteoarthritis.

Methods: Data were obtained retrospectively from the medical records of patients diagnosed with KOA between January 1, 2019, and September 1, 2019. Patients who received intra-articular ozone injections (n=27) according to a routine protocol (two sessions per week for a total of four sessions, with doses of 25–20–10–10 gamma, respectively) were included. Evaluations were recorded at baseline, at the second week post-treatment (PT), and at 1 month and 3 months PT using the VAS, WOMAC, Lequesne Knee Index, and Nottingham Health Profile.

Results: The mean age of the patients (n=27) was 64.81±11.41 years (range: 44–82). Of the patients, 85.2% (n=23) were female and 14.8% (n=4) were male. All parameters showed significant improvement at 2 weeks PT compared with baseline, and the observed improvement persisted at the 1st and 3rd month PT evaluations ($p<0.05$). No significant differences were found between the second week, 1st month, and 3rd month evaluations ($p>0.05$).

Discussion and Conclusion: Intra-articular ozone injection in patients with knee osteoarthritis may have positive effects on pain, functional status, and activities of daily living in the short and medium term. Larger-scale controlled clinical trials with longer follow-up periods are needed.

Keywords: Injection; knee osteoarthritis; ozone.

Osteoarthritis affects more than 240 million people worldwide, and the most common type is knee osteoarthritis. The knee is most frequently affected in up to 10% of males and 13% of females aged over 60 years. Knee osteoarthritis (KOA) is a common cause of pain and functional impairment and is frequently encountered in clinical practice within the spectrum of musculoskeletal disorders. As the global population continues to age, it remains a growing health concern of increasing significance. Risk factors include age, female sex, overweight and obesity, repetitive joint use, muscle weakness, and genetic factors [1].

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KOA is a complex disease that leads to disturbances in tissue homeostasis of the articular cartilage and changes in the subchondral bone [1]. While the pathogenesis of osteoarthritis has historically focused primarily on cartilage degeneration, recent research has underscored the inflammatory nature of KOA, characterized by inflammation in both the cartilage and synovium that progresses alongside degenerative processes. Proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-18, along with increased oxidative stress and metalloproteinase activity, are implicated in cartilage degeneration [2,3].

Various treatment modalities for KOA are available and are categorized as pharmacological and non-pharmacological approaches. Among non-pharmacological treatments, patient education, exercise, weight management, modification of daily life activities, and various physical therapy modalities are included. Within pharmacological treatments, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) may be the initial agents of choice. Narcotic analgesics can be considered for refractory cases. Additionally, interventional therapies such as intra-articular (IA) administration of corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and ozone injections are used [4,5]. IA treatments may be preferred in patients who do not respond to systemic medical treatment or who have contraindications to systemic medications [6].

Ozone is a colorless gas with a distinct odor and has been used as a therapeutic agent for various diseases since its discovery [7]. Ozone therapy is considered an effective treatment method for damaged articular cartilage in KOA. Ozone mitigates the inflammatory environment that damages the cartilage matrix and induces chondrocyte apoptosis in KOA. TNF-α is strongly associated with joint and bone damage, and ozone therapy reduces TNF-α concentrations, thereby decreasing other proinflammatory cytokines that perpetuate the chronic inflammatory process. By increasing the activity of the superoxide dismutase enzyme, ozone therapy accelerates the breakdown of free oxygen radicals, thus slowing the degenerative process. It also exerts analgesic and anti-inflammatory effects through the inhibition of phospholipase A2 [8].

As a result, when traditional treatments are compared with ozone therapy for knee osteoarthritis, traditional approaches mainly focus on symptom relief and slowing disease progression, whereas ozone therapy aims to utilize its anti-inflammatory and regenerative properties. Comparisons of ozone therapy with other treatment methods for knee osteoarthritis have been reported. The effect of ozone appears more rapidly; however, its duration of efficacy has been observed to be shorter than that of hyaluronic acid and PRP injections [9,10]. It has been emphasized that combining ozone therapy with physical therapy modalities and exercise enhances overall treatment efficacy [11].

Although the efficacy of ozone therapy in the treatment of KOA has been demonstrated, its use as a therapeutic agent remains controversial [12]. In recent years, ozone therapy has been used in the treatment of acute and chronic knee osteoarthritis in Europe, with studies reporting rapid pain relief, reduced swelling, and improved mobility. However, the exact mechanisms, optimal application frequency, and dosage of ozone in KOA treatment remain unclear [13]. In various studies, the most effective dose for reducing superoxide dismutase and IL-6 levels has been reported as 40 mcg. Accordingly, it has been emphasized that the optimal anti-inflammatory dose is 40 mcg, while the anti-inflammatory effect decreases as the dose is reduced to 20 mcg. When the dose exceeds 40 mcg, a reduction in anti-inflammatory efficacy has been observed [14]. In another study conducted in patients with rheumatoid arthritis, TNF-α concentrations in synovial fluid were evaluated, and TNF-α levels were found to decrease most effectively at a dose of 40 mcg, followed by a decrease at a dose of 20 mcg [15].

In the present study, patients were treated with an initial dose of 25 mcg for anti-inflammatory effect, followed by 20 mcg, and received an induction dose of 10 mcg in the final two injections. The aim of this study was to evaluate the short- and medium-term effects of intra-articular ozone injection on pain, functional status, and activities of daily living in patients with knee osteoarthritis.

Materials and Methods

Data for this study were retrospectively collected by reviewing the medical records of patients diagnosed with KOA who underwent IA ozone injection between January 1 and September 1, 2019. The study included patients with KOA stages 2–4 according to the Kellgren–Lawrence classification who received a total of four sessions of ozone injections at 4-day intervals (n=27). In the first session, 10 ml of 25 mcg; in the second session, 10 ml of 20 mcg; and in the third and fourth sessions, 10 ml of 10 mcg of IA knee ozone injection were administered. Dose selection aimed to provide relatively anti-inflammatory doses in the first two applications and relatively inductive doses in the last two applications.

During the treatment period, patients were provided with a home exercise program that included isometric strengthening exercises and joint range-of-motion exercises targeting the knee joint. All patients were screened for contraindications to ozone therapy, such as G6PDH deficiency, uncontrolled hyperthyroidism, and

Table 1. Demographic data

Demographic parameter	Mean (range)	
Age (years)	67 (44-82)	
Body mass index (kg/m^2)	29 (24-36)	
	n	**%**
Gender		
Male	4	14.8
Female	23	85.1
Kellgren lawrence stage		
Stage 2	8	29.6
Stage 3	10	37.03
Stage 4	9	33.3
Heat sensation		
Present	4	14.8
Absent	23	85.1
Joint effusion		
Present	11	40.74
Absent	16	59.25
Crepitus		
Present	27	100
Absent	0	0

pregnancy. Furthermore, patients were evaluated in terms of age, sex, body mass index, presence of increased heat, presence of crepitus, and presence of effusion. Increased heat in the knee was detected by palpation. Crepitus was identified by palpation during joint movement. The ballottement test was applied to determine the presence of knee effusion.

All injections were administered by the same clinician using the same technique, with patients in the seated position and under appropriate sterilization conditions. During the injection, a 10 cc ozone-resistant syringe and a 21-gauge, 16 mm needle were used. The injection was administered via an anterolateral approach to the knee. Patients were informed about the treatment, and written consent was obtained. Patients who had received any physical therapy modalities or IA injection methods within the previous six months, as well as those who used NSAIDs, analgesic drugs, or any supportive oral joint preparations or lower limb orthoses during the treatment period, were excluded from the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Health Sciences University Hamidiye Scientific Research Ethics Committee on June 4, 2021, with approval number 19/14.

Statistical Analysis

Patient records were evaluated at baseline (T0), at 2 weeks (T1), at 1 month (T2), and at 3 months (T3) post-treatment. The evaluation included the Visual Analog Scale (VAS) for resting pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Lequesne Knee Index for functionality, and the Nottingham Health Profile for quality of life. The Turkish validity and reliability of these instruments have been scientifically established [16–18]. Follow-up assessments were conducted by the same physician.

Statistical analysis was performed using the SPSS 22.0 Statistical Program. Due to the retrospective nature of the study and the available data from 27 patients, a sample size analysis was not performed. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Descriptive statistics are presented as median values with minimum and maximum values. As the data did not show a normal distribution, the Friedman test was used for intragroup comparisons. In post hoc analysis of significant results, the Wilcoxon test was applied for pairwise comparisons.

Results

The mean age of the 27 patients included in the study was 64.81±11.41 years (range 44–82). Of these patients, 23 were female and 4 were male. Other demographic characteristics of the patients are summarized in Table 1.

Table 2. Pre-treatment and post-treatment evaluations

Assessment parameter	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	p^*	$p^{\#}$ (α)	$p^{\#}$ (β)	$p^{\#}$ (□)
VAS	7.37±2.25	4.55±2.84	4.59±3.07	4.33±3.12	**0.001**	**0.001**	**0.001**	**0.001**
WOMAC	58±16.29	47.03±16.11	46.74±16.25	46.55±17.80	**0.001**	**0.001**	**0.001**	**0.001**
Nottingham	42.55±15.23	44.48±14.92	44.88±14.77	45.40±13.84	**0.001**	**0.001**	**0.001**	**0.001**
Lequesne	14.07±4.74	11.81±4.64	11.70±4.71	11.62±5.43	**0.001**	**0.001**	**0.001**	**0.001**

*: Friedman test; #: Wilcoxon test; (α): Pre-Treatment to 2 Weeks Post-Treatment; (β): Pre-Treatment to 1 Month Post-Treatment; (ɤ): Pre-Treatment to 3 Months Post-Treatment. VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; Pre-Treatment: T0; Post-Treatment: T1 (2 weeks; T2 (1 month); T3 (3 months); SD: Standart deviation.

Compared with the pre-treatment period, a statistically significant improvement was observed at 2 weeks post-treatment ($p<0.05$). This positive effect was found to persist at the 1st- and 3rd-month evaluations (Table 2). No significant differences were observed between the evaluations at 2 weeks, 1 month, and 3 months ($p>0.05$). No adverse effects were observed.

Discussion

The treatment of osteoarthritis remains an active area of research, with various therapeutic options under investigation. In this study, we examined the effects of intra-articular ozone therapy, which is low-cost and associated with minimal side effects, on pain scores, functional status, and activities of daily living in patients with knee osteoarthritis. It was observed that the significant positive effect, which began at the second week compared with baseline, persisted up to the third month.

In a study conducted by Lopes de Jesus et al. [19] in 2017, 61 patients were treated with eight sessions of 10 ml of 20 mcg/ml intra-articular ozone injection, while a second group of 35 individuals received eight sessions of intra-articular oxygen therapy. Patients were evaluated using the Visual Analog Scale (VAS), Lequesne Index, and Short Form-36 (SF-36) at baseline and at 1, 2, and 4 months. The results demonstrated a significant improvement in patients treated with intra-articular ozone compared with the placebo group. Unlike our study, eight sessions were administered with a constant dose of 20 mcg of ozone in each session, and a control group was included. In addition, the treatment protocol began with four sessions at 25 mcg and ended with a maintenance dose of 10 mcg. There is currently no established standard regarding the number of sessions or the optimal dosage of ozone in intra-articular ozone therapy.

In a study by Hashemi et al. [20] in 2016, 72 patients with stage 2–3 knee osteoarthritis were divided into two groups. The first group received eight sessions of 10 ml of 40 mcg/ml intra-articular ozone and 5 ml of periarticular ozone, with three sessions in the first week, two sessions in the second week, and the remaining three sessions administered weekly. The second group underwent genicular nerve block and intra-articular radiofrequency treatment. Pain scores were evaluated at baseline and at the third month. Both groups showed improvement, and no significant difference was observed between them. In contrast to our study, periarticular ozone injection was applied in addition to intra-articular ozone injection. Comparative studies are needed to evaluate the relative effectiveness of intra-articular and periarticular ozone injections. It should also be noted that this study included patients with stage 2–3 knee osteoarthritis.

In addition to comparisons with placebo and non-pharmacological treatments, ozone injection has also been compared with other infiltrative treatment modalities. In 2017, Duymus et al. [21] conducted a study including 102 patients with stage 2–3 knee osteoarthritis. The first group received four sessions of 2 ml of lidocaine and 15 ml of 30 mcg/ml intra-articular ozone injection. The second group received two sessions of platelet-rich plasma (PRP), and the third group received a single dose of 1.6 million Dalton hyaluronic acid (HA). Patients were evaluated using VAS and WOMAC scores at baseline and at 1, 3, 6, and 12 months. All three groups demonstrated similar positive outcomes at 1 month; however, at 3 months, the PRP and HA groups continued to improve, whereas the effect in the ozone group diminished. At 6 months, the most pronounced response was observed in the PRP group compared with the HA group, and the effect of ozone therapy had completely disappeared. In contrast to these findings, in our study, the positive effects of intra-articular ozone therapy that began at the second week persisted up to the third month. Further studies are required to clarify the duration of the therapeutic effect of ozone injection.

In a study by Hashemi et al. [22] in 2015 including 80 patients, participants were divided into two groups. The first group received three sessions of 5 ml of 15 mcg/ml intra-articular ozone injection, whereas the second group received three sessions of 12.5% intra-articular hypertonic dextrose. Patients' pain and WOMAC scores were assessed at baseline and at the third month. Both groups showed significant improvement, with no significant difference between them. In this study, ozone injection was administered in 5 ml doses. Findings from previous studies indicate considerable variability in the standard dosage and number of sessions for ozone injection.

In 2019, Ata et al. [23] compared intra-articular ozone therapy with polynucleotide gel injection in patients with stage 2–3 knee osteoarthritis. The first group of 30 patients received a total of four sessions at 1-week intervals, with doses starting at 20 ml and 20 mcg/ml, followed by 15 mcg/ml, 10 mcg/ml, and 10 mcg/ml. The second group of 32 patients received a single 2 ml injection of 20 mg/ml polynucleotide gel. Both groups were evaluated for pain scores at baseline and at 5 and 12 weeks. Significant improvement was observed in both groups, with no significant difference between them. Unlike our study, a 20 ml ozone injection with varying doses was used, and the sessions were scheduled weekly. Further studies are needed to determine the optimal intervals between ozone injection sessions.

The primary limitation of our study is its retrospective design. Another limitation is the absence of a comparison between intra-articular ozone therapy and other treatment modalities. Patient responses were evaluated up to the 3-month follow-up period, indicating the need for longer-term follow-up studies.

Conclusion

In patients with knee osteoarthritis, intra-articular ozone injection may have positive effects on pain, functional status, and activities of daily living in the short and medium term. Further large-scale and comprehensive studies are needed to determine the standard dose, volume, and number of sessions for intra-articular ozone therapy, its effectiveness across different disease stages, and the duration of its therapeutic effects.

Ethics Committee Approval: The study was approved by University of Health Sciences Hamidiye Scientific Research Ethics Committee (No: 19/14, Date: 04.06.2021).

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