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Original Article

Comparison of intra-articular injection of ozone combined with hyaluronic acid versus platelet-rich plasma injection for treating knee osteoarthritis

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Abstract: Introduction: This study aims to compare the therapeutic efficacy and safety of intra-articular injection of ozone combined with hyaluronic acid (HA) *versus* platelet-rich plasma (PRP) injection in patients with mild-to-moderate knee osteoarthritis (KOA). Methods: Patients were enlisted and randomly divided into two groups: the HA+ozone group and the PRP group. Then, the baseline data, NRS, WOMAC, and IKDC scores were recorded prior to injection (week 1), at the conclusion of one treatment session (week 5), at one month following injection completion (week 9), at three months following injection completion (week 17), and at six months following injection completion (week 29). Results: When compared to baseline, both strategies showed substantial improvements in NRS, WOMAC, and IKDC scores ($P<0.05$), at weeks 5, 9, 17, and 29. There were no discernible variations between the two groups, in terms of NRS, WOMAC, or IKDC scores at weeks 1, 5, 9, and 17. The PRP group's NRS, WOMAC total, WOMAC pain, and WOMAC function scores were lower than those of the HA+ozone group at week 29. Conclusion: The clinical symptoms of KOA can be reduced by intra-articular injections of ozone+HA and PRP. Both strategies show comparable short-term outcomes (within three months), but PRP shows longer-lasting (more than six months) therapeutic effects.

Keywords: Intra-articular injection, platelet-rich plasma, hyaluronic acid, ozone, knee osteoarthritis

Introduction

Osteoarthritis (OA) is a chronic degenerative disease characterized by loss of articular cartilage and alterations in subchondral bone structures, as well as abnormalities in adjacent fat pads, synovium, ligaments, and muscles [1]. As a major cause of disability, OA is increasingly prevalent in the elderly [2]. OA can occur in all joints, with knee osteoarthritis (KOA) making up about 80% of all arthritis cases [3]. The primary clinical manifestations of KOA include joint pain, stiffness, swelling, and in severe cases, joint deformities and limited mobility [4]. In China, the cumulative incidence of symptomatic KOA in the middle-aged and elderly population is 8.50%, with a significantly higher prevalence in women (11.20%), compared to men (5.60%) [5].

The treatment of KOA can be generally classified into surgical and non-surgical therapy. Surgical treatment is typically reserved for patients with severe KOA, which is characterized by joint deformities, intense pain, and structural damage [6]. In addition, total joint replacement surgery has a long recovery period, with inevitable risks and complications [7]. For patients with mild-to-moderate KOA, the symptoms can be alleviated through lifestyle modifications, exercise, and the use of oral or injectable medications. Oral non-steroidal anti-inflammatory drugs (NSAIDs) may provide short-term symptom relief, but its long-term use can lead to various adverse effects, including cardiovascular, gastrointestinal, and renal complications, especially in elderly patients. Intra-articular drug injections are a common non-surgical treatment for symptomatic KOA.

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It allows for the direct delivery of medication to the target tissue, maintaining the drug concentration in the joint capsule, and has been proven to be safe and effective [8]. Sodium hyaluronate is a common medication in intra-articular injections. Its primary component (hyaluronic acid [HA]) is an essential component of synovial fluid and the cartilage matrix, providing joint protection through lubrication. Furthermore, HA facilitates nutrient transport between the synovium and cartilage, and mitigates cartilage damage by regulating the proliferation, differentiation, and migration of chondrocytes [9]. Ozone (O_3) is a potent oxidizing agent, which has been used to alleviate synovial edema, inflammation, and pain, and improve the joint function and quality of life of KOA patients through intra-articular injection [10]. Ozone inhibits inflammatory responses by downregulating the TNF-α and TNF-R2 expression, upregulating TNF-R1 expression, and stimulating the release of IL-10 and FGF-β1 [11]. Furthermore, ozone preparation is cost-effective, and has been applied in orthopedic centers in Europe, with low risk of drug tolerance and infection [12]. Both intra-articular ozone and HA injections have advantages, including simple procedure, low cost, rapid recovery, and minimal side effects. Its combination is a feasible and effective treatment strategy, considering its distinct, but complementary and non-conflicting mechanisms.

The autologous platelet-rich plasma (PRP) is characterized by high platelet concentration, and contains a large number of growth factors that promote tissue repair and anti-inflammatory cytokines [13]. After injection into the joint space of the affected area, the activated platelets release a cascade of growth factors, which induces the proliferation and differentiation of mesenchymal stem cells, and promotes the regeneration of autologous cartilage cells. In addition, PRP enhances the extracellular matrix composition [14]. It is noteworthy that the autologous nature of PRP eliminates the risk of rejection reaction, and ensures high safety [15]. At present, no comparative studies have reported the efficacy of the intra-articular injection of ozone combined with HA and PRP. Thus, the present study aimed to evaluate and compare the pain and joint function after the intra-articular injection of the combination treatment (HA+ozone) versus PRP injection in patients with mild-to-moderate KOA.

Patients and methods

Patient recruitment

Patients with mild-to-moderate KOA were recruited from the Pain Clinic of the Brain Hospital, Liaocheng People's Hospital, Shandong Province, China, between November 2021 and February 2022. The study protocol was approved by the Ethics Committee of Liaocheng People's Hospital (Approval no.: 2021183), and registered with the Chinese Clinical Trial Registry (Registration no.: ChiCTR2100053667). A written informed consent was obtained from all participants before the injection treatments.

Inclusion and exclusion criteria

The diagnosis of KOA was based on the 2021 edition of the Guidelines for the Diagnosis and Treatment of Osteoarthritis [16]. Patients with recurrent knee pain within the past month were diagnosed as KOA when they met at least two of the following criteria: X-ray on weight bearing position (space narrowing, subchondral bone sclerosis or cystic changes, or osteophyte formation), middle-aged or older patients (>50 years old), have morning stiffness that last less than 30 minutes, and crepitus during joint movement.

The inclusion criteria were as follows: (1) 45-75 years old, (2) Kellgren-Lawrence (KL) grade I-III [17], (3) Body mass index (BMI) <30 kg/m^2, and (4) Stable knee joint without dislocation.

The exclusion criteria were as follows: (1) History of malignant conditions, such as bone tuberculosis or bone tumor; (2) Psychiatric disorders; (3) Coagulation disorders or current anticoagulant therapy; (4) Severe liver, kidney, heart, or lung dysfunction; (5) Allergic to lidocaine injection, sodium hyaluronate injection, or medical ozone; (6) Trauma to the target knee joint within the past six months; (7) History of intra-articular injections or surgery on the target knee joint within the past year; (8) Patients scheduled for total knee replacement within the next year; (9) Infection at the injection site.

The termination criterion was the occurrence of severe adverse reactions or life-threatening

events. The dropout criteria were as follows: loss to follow-up, severe adverse reactions or complications, poor compliance to treatment, or voluntary withdrawal during the study period. Patients were excluded when they failed to strictly adhere to the treatment protocol.

Treatment protocol

Basic patient information, such as age, gender, ethnicity, BMI, duration of knee joint pain (years), pain location, and KL grade, were recorded before the initial injection. A total of 64 patients were randomly assigned into two groups: the HA+ozone group and the PRP group. Patients in both groups were placed in the supine position, with the affected knee flexed at approximately 70-90°. After local anesthesia with 2% lidocaine, a needle was inserted into the joint space at approximately 1 cm below the lateral edge of the patellar tendon. The presence of synovial fluid confirmed the intra-articular placement. Patients in the HA+ozone group received an intra-articular injection of 10 mL of 30 μg/mL ozone and 2 mL of 20 mg/mL HA, while patients in the PRP group received an intra-articular injection of freshly prepared 4 mL PRP on the same day. The injections were administered once a week for five weeks as one complete treatment course. No additional therapeutic interventions were allowed except for analgesics, when necessary. The follow-up assessments were conducted by a blinded physician.

Drug preparation

Peripheral venous blood (8 mL) was collected from each patient using a disposable venous blood collection needle, and stored in a sterile container pre-filled with sodium citrate. Then, the blood sample was gently inverted for 3-5 times, and left to stand upright for 15-20 minutes before centrifugation at room temperature (20-25°C). The PRP was aseptically prepared using a dedicated PRP centrifuge (DD4-M; Xiangying Centrifuge Co., Ltd., Changsha, China) at 3,000-3,500 rpm for 10-15 minutes. Then, the middle layer of the yellow liquid (4 mL) was extracted using a 10 mL sterile syringe (0.80 mm) to obtain the freshly prepared PRP.

Medical ozone was generated using a medical ozone therapy device (ZAMT-80A, Zibo Qianyan Medical Equipment Co., Ltd.). The device was connected to a medical oxygen cylinder, and the oxygen flow rate was adjusted to 5 L/min. The ozone output concentration was set at 30 μg/mL. A 20 mL disposable sterile syringe was connected to the ozone generator outlet, allowing the gas to be automatically drawn.

Therapeutic assessment and follow-up

The therapeutic outcomes were evaluated using three validated tools: the numerical rating scale (NRS), the Western Ontario and McMaster Universities Osteoarthritis Index pain (WOMAC) score and International Knee.

Documentation Committee (IKDC) score. The NRS measures pain intensity on an 11-point scale from 0 to 10, categorizing pain into four levels: no pain (0), mild pain (1-3), moderate pain (4-6), and severe pain (7-10). The WOMAC comprises three subscales with a total of 24 items: pain (5 items), stiffness (2 items) and joint function (17 items). Each item was scored from 0 to 4. The WOMAC total score is equal to the sum of the scores for pain, stiffness and joint function dimensions, with a range of 0-96 points. A higher score indicates more severe symptoms of osteoarthritis. The IKDC system is a comprehensive scoring system jointly developed by the American Academy of Orthopaedic Surgeons and the European Knee Surgery and Arthroscopy Association for evaluating ligament and cartilage injuries related to the knee joint. This scoring system comprises two parts: subjective scoring and objective scoring. In this experiment, we selected the subjective scoring scale part of the scoring system. The IKDC system uses the subjective score component to evaluate knee symptoms, sports activity adaptation and functional capacity. The scoring method involves summing up the scores of individual items. This scoring scale is applicable to patients with various knee joint diseases and exhibits high reliability, validity, and sensitivity.

A physician blinded to the patient groupings conducted all the assessments. The scores were recorded at baseline (week 1) and at the end of the treatment course (week 5). Follow-up evaluations were conducted *via* telephone at one month (week 9), three months (week

Table 1. Comparison of baseline characteristics between the two groups

	PRP group (*n*=37)	HA+ozone group (*n*=36)	*p*-value
Gender	Male 13, Female 19	Male 16, Female 16	0.451#
Age (year)	60.19 ± 7.25	59.72 ± 8.03	0.807*
BMI (kg/m^2)	26.54 ± 3.47	26.88 ± 3.51	0.702*
KL grade			0.537※
I	13 (35.10%)	11 (16.70%)	
II	18 (48.60%)	17 (47.20%)	
III	6 (16.20%)	8 (26.00%)	
Affected knee joint			0.929#
Left	14 (43.80%)	14 (43.80%)	
Right	13 (40.66%)	14 (43.80%)	
Bilateral	5 (15.60%)	4 (12.50%)	
Duration of pain (year), median	2.00 (1.80, 4.50)	3.50 (1.10, 5.00)	0.383※
Pre-treatment NRS score	6.62 ± 0.98	6.50 ± 1.08	0.662※
Pre-treatment total WOMAC score	44.51 ± 6.70	45.75 ± 6.97	0.442*
Pre-treatment WOMAC pain score	10.89 ± 2.01	11.14 ± 2.03	0.662※
Pre-treatment WOMAC stiffness score	5.22 ± 0.95	5.56 ± 0.93	0.145※
Pre-treatment WOMAC knee function score	28.41 ± 4.62	29.06 ± 5.04	0.567*
Pre-treatment IKDC score	42.51 ± 4.30	42.81 ± 4.10	0.768*

Notes: PRP, platelet-rich plasma; HA, hyaluronic acid; BMI, body mass index; KL grade, Kellgren-Lawrence grade; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; IKDC, International Knee Documentation Committee; *, Student *t*-test; #, Pearson's chi-square test (χ^2), ※, Mann-Whitney U-test.

17), and six months (week 29) post-treatment.

Data analysis

The statistical analysis was performed using SPSS (version 26.0; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed in frequency and percentage. The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Student's *t*-test was used for normally distributed data, and Mann-Whitney *U*-test was applied for non-normally distributed data. Pearson's chi-square test was employed for categorical variables. Intra-group comparisons before and after treatment are conducted using the paired *t*-test, while inter-group comparisons are conducted using the independent samples *t*-test. Continuous data were presented as mean Â ± standard deviation ($\bar{x}$ ± s) or median (M) and interquartile range (IQR), while categorical data were presented as frequency and percentage, and inter-group comparisons are conducted using the Chi-square test or Fisher's exact test. A *p*-value of <0.05 was considered significant.

Results

Comparison of baseline data between the two groups

A total of 64 patients, with 73 affected knees, were included for the present study (PRP group: 32 patients, 37 knees; HA+ozone group: 32 patients, 36 knees). The baseline characteristics, which included age, gender, height, weight, BMI and KL grade, had no significant differences between the two groups (**Table 1**). Next, the joint pain and function before and after treatment were evaluated using the NRS (**Table 2**), WOMAC (**Tables 3**-**5**) and IKDC (**Table 6**) scores. The results revealed no significant differences in baseline NRS scores for knee pain, WOMAC subscale scores, and IKDC scores before treatment between the two groups (week 1, *P*>0.05).

Clinical efficacy

Both groups presented with significant reductions in NRS and WOMAC scores at week 5 (end of treatment), week 9 (one month post-treatment), week 17 (three months post-treat-

Table 2. Comparison of NRS scores between the two groups

	Week 1	Week 5	Week 9	Week 17	Week 29
PRP group	6.62 ± 0.98	3.78 ± 0.75	2.84 ± 0.50	2.35 ± 0.63	1.95 ± 0.58
HA+ozone group	6.50 ± 1.08	3.69 ± 0.82	2.75 ± 0.55	2.58 ± 0.81	2.42 ± 0.65
Z-score	-0.438	-0.355	-0.753	-1.670	-3.363
p-value	0.662※	0.722※	0.451※	0.095※	0.001※,a

Notes: NRS, numeric rating scale; PRP, platelet-rich plasma; HA, hyaluronic acid; ※, Mann-Whitney U-test; a, $P<0.05$.

Table 3. Comparison of WOMAC total scores between the two groups

	Week 1	Week 5	Week 9	Week 17	Week 29
PRP group	44.51 ± 6.70	26.95 ± 3.00	24.30 ± 2.13	22.73 ± 2.19	19.19 ± 2.61
HA+Ozone group	45.75 ± 6.97	27.39 ± 3.06	24.89 ± 1.77	23.56 ± 1.84	22.92 ± 2.48
T-value	-0.773	-0.624	-1.288	-1.739	-6.253
p-value	0.442*	0.535*	0.202*	0.086*	0.000*,a

Notes: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PRP, platelet-rich plasma; HA, hyaluronic acid; *, Student *t*-test; a, $P<0.05$.

Table 4. Comparison of WOMAC pain scores between the two groups

	Week 1	Week 5	Week 9	Week 17	Week 29
PRP group	10.89 ± 2.01	6.27 ± 1.10	6.03 ± 1.04	5.57 ± 1.07	4.81 ± 1.18
HA+Ozone group	11.14 ± 2.03	6.44 ± 1.23	6.00 ± 0.96	5.97 ± 0.97	5.78 ± 1.02
Z-score	-0.436	-0.588	-0.336	-1.701	-3.482
p-value	0.662※	0.557※	0.737※	0.089※	0.000※,a

Notes: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PRP, platelet-rich plasma; HA, hyaluronic acid; ※, Mann-Whitney U-test; a, $P<0.05$.

Table 5. Comparison of WOMAC stiffness scores between the two groups

	Week 1	Week 5	Week 9	Week 17	Week 29
PRP group	5.22 ± 0.95	3.30 ± 0.57	3.03 ± 0.69	2.84 ± 0.73	2.51 ± 0.61
HA+Ozone group	5.56 ± 0.93	3.28 ± 0.62	3.14 ± 0.64	2.92 ± 0.55	2.75 ± 0.50
Z-score	-1.459	-0.082	-0.619	-0.471	-1.796
p-value	0.145※	0.935※	0.536※	0.638※	0.073※

Notes: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PRP, platelet-rich plasma; HA, hyaluronic acid; ※, Mann-Whitney U-test.

Table 6. Comparison of WOMAC joint function scores between the two groups

	Week 1	Week 5	Week 9	Week 19	Week 29
PRP group	28.41 ± 4.62	17.38 ± 2.68	15.24 ± 2.19	14.43 ± 2.47	11.86 ± 2.88
HA+Ozone group	29.06 ± 5.04	17.67 ± 2.96	15.69 ± 1.72	14.67 ± 1.90	14.39 ± 2.42
T-value	-0.575	-0.437	-0.977	-0.454	-4.051
p-value	0.567*	0.664*	0.332*	0.651*	0.014*,a

Notes: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PRP, platelet-rich plasma; HA, hyaluronic acid; *, Student *t*-test; a, $P<0.05$.

ment), and week 29 (six months post-treatment), when compared to baseline ($P<0.05$). Consistently, the IKDC scores significantly increased at weeks 5, 9, 17, and 29 in both

groups, when compared to baseline (P<0.05), suggesting that both interventions ameliorated the KOA symptoms.

Next, the therapeutic effects were compared between the two groups. There was no significant difference in NRS, WOMAC and IKDC scores at weeks 1, 5, 9, and 17 (P>0.05). Intriguingly, the NRS scores, WOMAC total scores, and WOMAC pain scores were significantly lower, while the IKDC scores were higher at week 29 (six months post-treatment) in the PRP group, when compared to the HA+ozone group (P<0.05) (Supplementary Table 1). However, there were no differences in WOMAC stiffness and function scores at any time-point between the two groups (**Tables 4** and **5**). The repeated measures ANOVA indicated significant time effects and group effects for the NRS and WOMAC total scores, suggesting a significant difference in trends between the two groups, and an interaction between the time points and group assignment (NRS score time: F=606.30, P<0.001, group: F=5.20, P=0.005; WOMAC total score time: F=747.40, P<0.001, group: F=3.60, P=0.039).

Adverse reaction

All patients completed the injections as required by the protocol. Two patients (one patient from each group) experienced joint pain and swelling after the injection, which were resolved after cold compress treatment. No severe adverse reactions, such as infections, muscle atrophy, abnormal tissue proliferation, deep vein thrombosis of the lower limbs, or cardiovascular events, were observed in any of the groups during the follow-up period.

Discussion

The present study compared the therapeutic efficacy of the intra-articular injection of ozone (O_3) combined with HA *versus* PRP for mild-to-moderate KOA. The present findings revealed significant improvements in NRS, WOMAC, and IKDC scores in both groups, when compared to baseline levels, indicating the safety and efficiency of these two intervention strategies. It is noteworthy that in the follow-up results at week 29, there were 2.5 times and 3.5 times increases in NRS and WOMAC total scores, respectively, when compared to baseline. In addition, the IKDC scores at the final follow-up were approximately 60% of the baseline values. These results confirm that both treatment strategies were effective options for the management of KOA. The drugs and biologics injected into joints mainly include the following: corticosteroids, hyaluronic acid, platelet-rich plasma (PRP), ozone, mesenchymal stem cells, and stromal vascular fraction. Methylprednisolone acetate can significantly alleviate early pain in patients. Studies have shown that its efficacy peaks around 2 weeks after intra-articular injection and can last for approximately 24 weeks [18]. A systematic review and meta-analysis study revealed that intra-articular injections of hyaluronic acid significantly alleviated pain in patients with early moderate arthritis, compared to injections of saline solution, with no adverse events observed during a 6-month follow-up [19]. Platelet-rich plasma (PRP) is rich in growth factors. After activating platelets, these factors are released at the injury site to promote tissue healing. A clinical trial found that a single injection of PRP achieved satisfactory clinical efficacy, with 84.2% of patients experiencing symptom relief [20]. A randomized, double-blind, placebo-controlled study conducted by Giombini on intra-articular injections of ozone and placebo in the knee joint showed that 8 weeks of weekly treatment with 20 μg/mL ozone significantly reduced pain intensity and improved joint function [21]. Research related to mesenchymal stem cells and stromal vascular fraction is still in its infancy.

The combination strategy of using HA to protect the cartilage and ozone to reduce inflammation has been previously investigated in studies on KOA [22]. The study conducted by Luo *et al.* showed that a 25-30 μg/mL concentration of ozone can provide the best outcomes [23]. Thus, a concentration of 30 μg/mL was employed for the joint injections. A meta-analysis revealed that the therapeutic effect of intra-articular ozone injections was effective in the short term (1-3 months), but this effect would decline within 3-6 months in patients with mild-to-moderate KOA (KL grades I-III) [24]. Furthermore, a clinical trial that compared HA and ozone combination therapy with HA monotherapy revealed that the combination provided superior pain relief and greater improvement in knee joint function [25]. These results are consistent with the present data results, validating the efficacy of the HA and ozone combination strategy.

It is noteworthy that the PRP injections had superior outcomes at six months post-treatment, when compared to the ozone combined with HA injection. Up until week 17, there were no significant differences between the two groups. However, at the final follow-up (week 29), the NRS score was approximately 20% lower in the PRP group, when compared to the HA+ozone group (1.95 *vs.* 2.42). This result is supported by other related studies. It has been proven that PRP can ameliorate pain and improve joint function for at least one year, with the most pronounced benefits observed at six months. A randomized controlled trial that compared PRP and a placebo revealed significant improvements in pain scores at one and six months in the PRP group [26, 27]. Medhat *et al.* conducted a prospective, double-blind, randomized controlled study with a three-year follow-up period. That study revealed that PRP can provide longer symptom relief, extended functional improvement, and fewer reinjection requirements, when compared to HA [28]. Accumulated studies have confirmed that PRP outperforms HA in both short-term functional recovery, and long-term pain relief and functional improvement, without increasing the risk of adverse events [29, 30]. A clinical trial that compared PRP and ozone intra-articular injections revealed comparable short-term efficacy within the first month, and reported that PRP exhibited better effects at three and six months post-treatment [31]. Duymus *et al.* reported that the ozone treatment effect on KOA diminished at three and six months, when compared to sustained therapy with PRP and HA [32]. Furthermore, Seyed *et al.* reported that ozone injections can provide favorable benefits at two months, when compared to PRP and HA, and that PRP injections outperformed HA and ozone at 12 months [33]. Moreover, Arias *et al.* reported that the therapeutic effect of ozone peaked at approximately one month, and significantly declined by three months [34]. The present data revealed consistent results, in which the efficiency of ozone combined with HA declined at week 29, when compared to the sustained effects of PRP.

The present study had several limitations. The relatively small sample size and single-center recruitment may have introduced selection bias, and limited the generalizability of the findings. Furthermore, the heterogeneity of patients, such as gender, BMI, or KOA severity, should be further clarified. Thus, a more comprehensive and rigorous study with a sufficient sample number to evaluate the specificity of the therapeutic outcomes of PRP, the combination of HA and ozone, HA alone, or ozone alone would provide greater clinical significance and deeper insight into its treatment efficacy.

Conclusions

For patients with mild-to-moderate KOA, both the injection of intra-articular PRP and the combined injection of HA and ozone can alleviate pain, reduce stiffness, and improve joint mobility. Although both treatments have short-term benefits (within three months post-treatment), PRP-based injections provided longer-lasting effects, when compared to the combined injection of HA and ozone.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Comparison of IKDC scores between the two groups

	Week 1	Week 5	Week 9	Week 17	Week 29
PRP group	42.51 ± 4.30	54.49 ± 4.52	59.62 ± 4.71	65.54 ± 4.18	73.27 ± 2.90
HA+Ozone group	42.81 ± 4.10	53.58 ± 4.66	58.61 ± 4.73	65.00 ± 4.75	71.47 ± 3.49
T-value	-0.297	-0.841	-0.915	-0.517	2.389
P-value	0.768*	0.403*	0.363*	0.607*	0.020*,a

Notes: IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; HA, hyaluronic acid; *, Student *t*-test; [a], $P<0.05$.