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Original Article

Effects of joint irrigation combined with ozone injection on bone metabolism, inflammatory factors, and joint function in knee osteoarthritis

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Abstract: Objective: To explore the effects of joint irrigation combined with ozone injection on bone metabolism, inflammatory factors, and joint function in patients with knee osteoarthritis (KOA). Method: In this retrospective study, a total of 132 KOA patients admitted to No. 215 Hospital of Shaanxi Nuclear Industry from October 2019 to July 2021 were enrolled. Among them, 62 patients received arthroscopic irrigation alone were assigned into a control group, and the remaining 70 patients who received arthroscopic irrigation combined with ozone injection were assigned into an observation group. Therapeutic efficacy and adverse reactions during the treatment were compared in the two groups. Bone metabolism, inflammatory factor levels and joint function of patients before and after treatment were observed; patients were further divided into a good prognosis group and a poor prognosis group regarding their prognosis. Multivariate analysis was performed to explore the independent risk factors affecting prognosis. Results: After treatment, compared to the control group, the total effective rate of the observation group was higher ($P<0.05$), and there was no notable difference in the incidence of adverse reactions between the two groups ($P>0.05$). The bone metabolism indexes, osteocalcin (OC) and osteoprotegerin (OPG), in the observation group were also significantly higher ($P<0.05$), while the level of nuclear transcription factor κB receptor activator ligand (RANKL) in the observation group was markedly lower. The inflammation level in the observation group was lower ($P<0.05$). Lysholm score in the observation group was strikingly higher ($P<0.05$), while its Western Ontario McMaster (WOMAC) score and visual analogue scale (VAS) were lower ($P<0.05$). The observation group had a lower rate of poor prognosis ($P<0.05$). Age (OR: 1.786, 95% CI: 1.347-2.370), disease duration (OR: 1.132, 95% CI: 1.002-1.279), VAS after treatment (OR: 2.316, 95% CI: 1.089-4.925), and post-treatment IL-6 (OR: 1.186, 95% CI: 1.017-1.382) were all independent risk factors for poor prognosis. Conclusion: Joint irrigation combined with ozone injection shows good efficacy in the treatment of KOA, and could effectively relieve the clinical symptoms of patients, improve their bone metabolism indexes, and help the recovery of knee joint function.

Keywords: Joint irrigation, ozone injection therapy, KOA, bone metabolism, joint function

Introduction

Knee osteoarthritis (KOA), a highly disabling disease that seriously affects the quality of life and independent living ability of middle-aged and elderly people, has a global prevalence of more than 15% and affects more 40% of the population aged over 40 [1, 2]. The incidence of KOA increases with age [3], and KOA has ranked the first in the osteoarthritis in all parts of the body. It is characterized by articular cartilage destruction, subchondral sclerosis or cystic degeneration, intrachondral bone hyperplasia and osteophyte formation, with the clinical symptoms of limited activity, joint swelling, and pain [4]. The etiology of KOA is complex and is related to various factors including genetics, age, gender, obesity, trauma and inflammation [5].

So far, KOA has no cure, and the main purpose of treatment is merely to relieve pain, improve or restore the function of the knee joint, correct the varus and valgus deformity of the joint, and prolong the life of joints [6]. Knee replacement surgery is considered to be the most effective

treatment for advanced KOA, but it also poses a great burden for patients, including large surgical trauma and the risks of prosthesis loosening, deep vein thrombosis, or infection. Therefore, the clinical focus has gradually shifted to the prevention and treatment of the disease in its early stage [7, 8]. Compared to other surgical methods, arthroscopic debridement has the advantage of less damage, and it can flush the joint cavity and treat the damaged structure under the monitoring of the arthroscopic system [9]. This minimally invasive technique can relieve knee pain, prevent further deterioration of joint symptoms, and improve joint function [10]. However, postoperative pain, swelling and limited joint movement can affect the functional recovery of the knee and the efficacy of surgical treatment [11]. Ozone can inhibit inflammation by releasing antioxidants to achieve an anti-inflammatory effect, and at the same time directly act on nerve endings, inhibit neurons from releasing pain signals, and achieve an analgesic effect. Studies have shown that injecting ozone in the joint cavity could delay the degeneration of articular cartilage in the KOA rat model, which is an effective treatment for KOA [12].

In this study, joint irrigation combined with ozone injection was applied to treat KOA to observe the curative effect of the combined treatment, as well as their effects on the patient's bone metabolism and other indicators.

Methods and information

Clinical information

In this retrospective study, 132 KOA patients admitted to No. 215 Hospital of Shaanxi Nuclear Industry from October 2019 to July 2021 were enrolled and their clinical data were analyzed. Among them, 62 patients who received arthroscopic irrigation alone were assigned into the control group (27 males and 35 females), with an average age of (62.48±7.29) years old and an average disease duration of (20.13±7.23) months. Another 70 patients treated with arthroscopic irrigation combined with ozone injection were included in the observation group (34 males and 36 females), with an average age of (63.46±6.05) years old and an average course of disease (18.19±6.84) months. This study was approved by the medical ethics committee of No. 215 Hospital of Shaanxi Nuclear Industry (No. 20190455).

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the KOA diagnostic criteria established by the American College of Rheumatology [13]; Patients who had no KOA-related treatment within the past week; Patients with good treatment compliance; and Patients with complete clinical data.

Exclusion criteria: Patients with osteoarthritis in other joints; Patients with combined systemic infection or local rash and infection of the knee joint; Patients with obvious tears in meniscus and ligament; Patients who were intolerant or unwilling to be treated; Patients with Grade III KOA or above according to Kellgren-Lawrence grading based on X-ray, and severe deformity of the knee joint; patients with knee joint tumor, rheumatoid arthritis, bone tuberculosis, suppurative and complications affecting the knee joint structure; or patients who had undergone knee joint cavity surgery.

Treatment plans

Patients in the Control Group were treated with arthroscopic joint debridement. Briefly, the patients were placed in the supine position to sag naturally after anesthesia, and epinephrine in 0.9% sodium chloride was injecteded to expand the knee joint. The anteromedial and anterolateral approaches of the knee joint were selected, and longitudinal incisions were made on both sides of the patellar ligament at the knee joint space. During the operation, cartilage debris, cartilage detachment, loose bodies, synovial hyperemia and edema, meniscus injury, ligament injury, and osteophyte hyperplasia in the intercondylar fossa were closely observed. Subsequently, 3000 mL of 0.9% sodium chloride injection was used to flush the joint cavity with negative pressure, and hyperplastic synovium was planned and excised to completely remove the hyperplastic osteophytes and loose bodies. The damaged articular cartilage and meniscus were then trimmed and polished. After surgery, an elastic bandage should be applied for compression fixation.

For patients in the Observation Group, additional ozone was injected on the basis of the Control Group. After approximately 10 days,

when surgical incision was healed, intra-articular injection of ozone (20 mL ozone at a concentration of 40 μg/mL) was applied once a week. Four consecutive injections (4 weeks) were given as a course of treatment.

Efficacy evaluation criteria

The curative effect was evaluated for all patients 3 months after treatment, and was divided into three grades: markedly effective, effective and ineffective. Markedly effective: symptoms basically disappeared, friction noise in the joint was significantly reduced, joint function was basically recovered, related examination results were significantly improved, and the patients could participate in labor and work normally; Effective: clinical symptoms, knee joint function and related examinations were improved, with no pain at rest and tolerable pain during activity, and patients were able to take care of themselves and even conduct light physical labor; Ineffective: the clinical symptoms were not alleviated or even worsened, and it was difficult for patients to engage in physical activity. The total clinical effective rate = markedly effective rate + the effective rate.

Scale evaluation criteria

The Lysholm knee joint score was used to evaluate the functional status of the knee joint of patients [14], which consisted of 8 questions including pain, instability, and squatting posture, with a total score of 100 points, and score less than 70 points indicated poor functional state of the knee joint. Knee function and joint pain were evaluated by Western Ontario McMaster (WOMAC) index and visual analogue scale (VAS) score of osteoarthritis. The WOMAC includes three dimensions: joint function, pain, and stiffness [15], with a score range of 0-100, and higher score indicates more severe joint dysfunction. Visual analogue scale (VAS) also has a total score of 10, and a decrease in VAS score shows pain relief.

Observation indicator

(1) The therapeutic efficacy 3 months after the treatment was evaluated and compared between the two groups. (2) The adverse reactions in the two groups of patients were counted and compared. (3) The patients' joint function and pain improvement before and 3 months after treatment were evaluated by Lysholm knee joint score, WOMAC index, and VAS score, respectively. (4) 5 ml of venous blood was collected before and 3 months after treatment, centrifuged (1500×g at 4°C for 10 min) to obtain the serum, and the bone metabolism indices, osteocalcin (OC), osteoprotegerin (OPG), nuclear transcription factor KB receptor activator ligand (RANKL), and the levels of inflammatory markers IL-1β, IL-6, and TNF-α were detected using enzyme linked immunosorbent assay (ELISA). Kits for detection of OC, OPG, IL-1β, IL-6, TNF-α were purchased from Thermo Fisher in the United States (KAQ1381, EHTNFRSF11B, KAC1211, KAC1261, BMS223-4), RANKL detection kits were purchased from Wuhan Elabscience Company (E-EL-H5558c); (5) Lysholm knee joint score was used to evaluate patients' knee joint scores 6 months after treatment. A score <70 points indicated poor prognosis, and ≥ 70 points indicated good prognosis. And the patients were further divided into a good prognosis group and a poor prognosis group, and multivariate analysis was performed to explore the independent risk factors affecting the prognosis of the patients.

Statistical methods

All collected data were statistically analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software, and figures were drawn using GraphPad Prism 7 (GraphPad Software, Inc., San Diego CA, USA). Counted data were expressed as X^2 and analyzed using chi-square test; All measured data were in line with normal distribution and expressed as mean ± SD. Intergroup comparison and comparison before and after treatment in the same group was performed with Student-t test and Paired t test, respectively. The independent risk factors affecting the prognosis of patients were analyzed by logistic regression. Significance level was $P<0.05$.

Results

Baseline information

Subjects were comparable due to insignificant differences in gender, age, course of disease, BMI, site of disease, X-ray grade, family history of knee arthritis, smoking, or heavy physical labor occupation between two groups ($P>0.05$, **Table 1**).

Table 1. Baseline data

	Control Group (n=62)	Observation Group (n=70)	X^2/t	P
Gender			0.334	0.564
Male	27 (43.55)	34 (48.57)		
Female	35 (56.45)	36 (51.43)		
Age (years)	62.48±7.29	63.46±6.05	0.844	0.400
Disease Duration (months)	20.13±7.23	18.19±6.84	1.583	0.116
BMI (kg/m^2)	24.7±3.11	25.2±3.15	0.916	0.362
Site of Disease			0.768	0.381
Unilateral Disease	38 (61.29)	48 (68.57)		
Bilateral Disease	24 (38.71)	22 (31.43)		
X-ray Kellgren-Lawrence Grading			1.212	0.546
I	22 (35.48)	19 (27.14)		
II	22 (35.48)	26 (37.14)		
III	18 (29.03)	25 (35.71)		
Family History of Knee Arthritis			1.204	0.273
Yes	15 (24.19)	23 (32.86)		
No	47 (75.81)	47 (67.14)		
Smoking			0.131	0.717
Yes	14 (22.58)	14 (20.00)		
No	48 (77.42)	56 (80.00)		
Heavy Manual Labor Occupation			0.507	0.477
Yes	16 (25.81)	22 (31.43)		
No	46 (74.19)	48 (68.57)		

BMI: Body Mass Index.

Table 2. Comparison of therapeutic efficacy

	Control Group (n=62)	Observation Group (n=70)	X^2	P
Markedly Effective	23 (37.10)	30 (42.86)	0.454	0.500
Effective	25 (40.32)	34 (48.57)	0.905	0.341
Ineffective	14 (22.58)	6 (8.57)	5.019	0.025
Total Effective Rate	48 (77.42)	64 (91.43)	5.019	0.025

Table 3. Comparison of adverse reactions

	Control Group (n=62)	Observation Group (n=70)	X^2	P
Joint Effusion	2 (3.23)	2 (2.86)		
Hematoma	4 (6.45)	3 (4.28)		
Joint Infection	1 (1.61)	0 (0.00)		
Total Adverse Reactions	7 (11.29)	5 (7.14)	0.684	0.408

Comparison of therapeutic efficacy

All patients were evaluated for the therapeutic effect after 3 months of treatment. The total effective rate of the observation group was significantly higher than that of the control group (P<0.05, 91.43% *vs.* 77.42%, **Table 2**).

Comparison of treatment-related adverse reactions

The total incidence of adverse reactions in the observation group was slightly lower than that of the control group (P>0.05, 7.14% *vs.* 11.29%), however, the difference between the two groups was not significant, as shown in **Table 3**.

Improvement of knee joint function and pain before and after treatment

The Lysholm score, WOMAC score, and VAS score of two groups were evaluated before and 3 months after treatment. Before treatment, there was no difference between two groups regarding the above three indicators (P>0.05). After treatment, the Lysholm scores of both groups were increased (P<0.05), while WOMAC scores and VAS scores were markedly decreased (P<0.05), and that increase in Lysholm

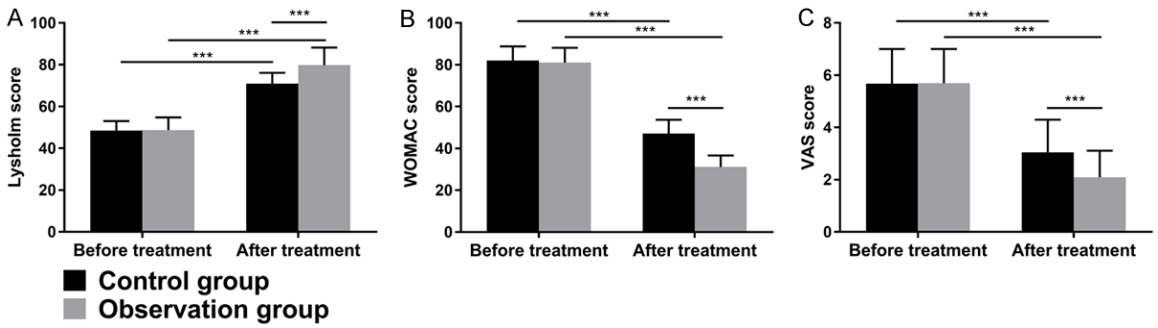

Figure 1. Improvement in knee joint function and pain before and after treatment. A. Lysholm score of the Observation Group after treatment was markedly higher than that of the Control Group (P<0.001). B. WOMAC score of the Observation Group after treatment was markedly lower than that of the Control Group (P<0.001). C. VAS score of the Observation Group after treatment was markedly lower than that of the Control Group (P<0.001). WOMAC: Western Ontario McMaster; VAS: Visual Analogue Scale. ***P<0.001.

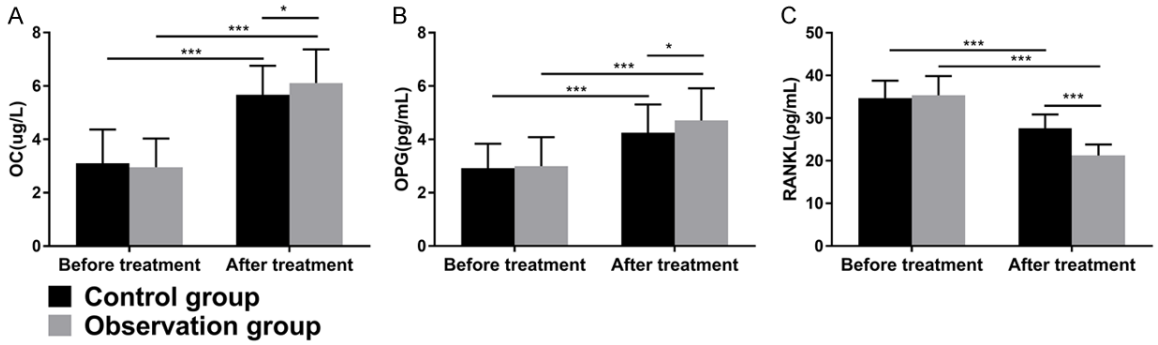

Figure 2. The effect of treatment regimen on bone metabolism. A. The OC of the observation group after treatment was markedly higher than that of the control group (P=0.035). B. OPG in the observation group was markedly higher than that in the control group after treatment (P=0.023). C. RANKL in the observation group was markedly lower than that in the control group after treatment (P<0.001). OC: Osteocalcin; OPG: Osteoprotegerin; RANKL: Nuclear Transcription Factor KB Receptor Activator Ligand. ***P<0.001.

and decline in WOMAC scores and VAS scores in the observation group were all greater than in the control group (P<0.05), as shown in **Figure 1**.

Effect of treatment regimens on bone metabolism

Before treatment, there were no statistical differences in bone metabolism indices, OC, OPG and RANKL, between the two groups of patients (all P>0.05). After treatment, OC and OPG went higher (P<0.05), and the up-regulation of the two in the observation group was significantly higher than in the control group (P<0.05). RANKL in both groups was markedly lower than before treatment (P<0.05), and the decline in the observation group was greater than in the control group (P<0.05), as shown in **Figure 2**.

Effect of treatment regimen on inflammation levels

No statistical difference was observed in the inflammatory factors IL-1β, IL-6 and TNF-α between two groups before treatment (all P>0.05). After treatment, those levels declined significantly in both groups (all P<0.05), and the reduction in the observation group was greater than in the control group (P<0.05, **Figure 3**).

Univariate analysis of patient prognosis

Patients were followed up for half a year. There were 18 patients with poor prognosis in the

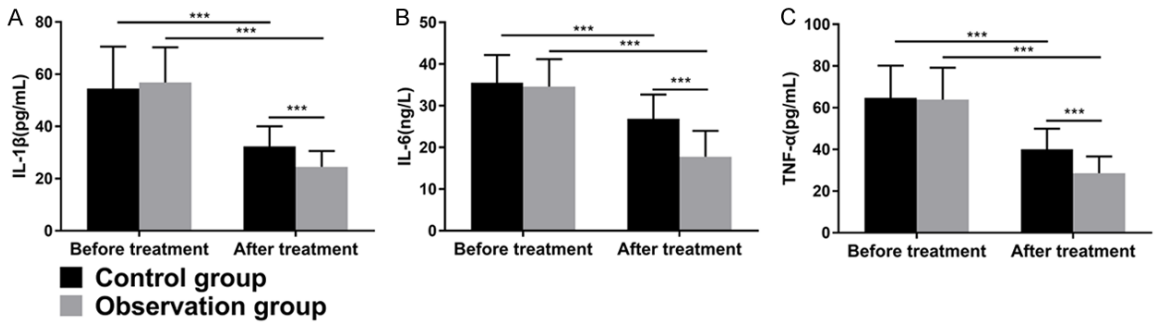

Figure 3. Effects of treatment regimens on inflammation levels. A. IL-1β of treatment regimens on inflaevidently lower than that in the control group after treatment (P<0.001). B. IL-6 in the observation group was evidently lower than that in the control group after treatment (P<0.001). C. TNF-α in the observation grouup was evidently lower than that in the control group after treatment (P<0.001). ***P<0.001.

control group and 8 in the observation group. According to the prognosis, the patients were divided into a good prognosis group and a poor prognosis group. Comparing the clinical data of the two groups, the two groups significantly differed in terms of age, disease course, WOMAC score after treatment, VAS score after treatment, OC after treatment, OPG after treatment, RANKL after treatment, IL-1β after treatment, IL-6 after treatment, TNF-α after treatment, and treatment method (P<0.05, **Table 4**).

Multivariate analysis

Logistic binary regression analysis was performed on the factors affecting the prognosis of patients, and it was found that age (OR: 1.786, 95% CI: 1.347~2.370), disease duration (OR: 1.132, 95% CI: 1.002~1.279), VAS score after treatment (OR: 2.316, 95% CI: 1.089~4.925) and IL-6 after treatment (OR: 1.186, 95% CI: 1.017~1.382) were independent risk factors for poor prognosis, see **Table 5**.

Discussion

Degenerative changes of articular cartilage is the main feature of knee osteoarthritis (KOA). On this basis, factors of cartilage fibrosis, formation of cracks on the cartilage surface, synovial hypertrophy, and osteophyte formation will cause obvious joint pain. In severe cases, joint deformities will occur and affect joint function [16]. Knee arthroscopic debridement, a minimally invasive debridement commonly used in clinical practice, can improve joint wear and meniscus damage, remove abnormally proliferated tissue, increase the active or passive range of motion, delay the development of osteoarthritis, and delay or even avoid knee replacement [17]. However, surgery can only temporarily control the clinical symptoms, not fundamentally reverse the pathologic process of KOA. Therefore, it is necessary to find a combination therapy according to individual conditions of the patients to achieve better efficacy [18]. Ozone injection into the knee joint cavity can directly act on the joint. As a substance with higher oxidative and water-soluble properties than oxygen, it is more soluble in blood and tissue fluid, can exert stronger oxidation and oxygen saturation effects, improves the internal environment of the joint cavity, promotes the elimination of inflammation and edema, and relieves pain [19].

The total effective rate in the observation group was significantly higher than that in the control group, and the incidence of adverse reactions in both groups was relatively low with no significant statistical difference. Pain and joint dysfunction are one of the main causes of impaired quality of life in KOA patients [20], so we compared the Lysholm score, WOMAC score and VAS score after 3 months of treatment between the two groups. After treatment, the observation group held a notably higher score of Lysholm while markedly lower score of WOMAC and VAS when compared to the control group, which suggested that combined therapy could better improve the knee joint function and pain of patients with high safety. Studies have shown that ozone could inhibit the synthesis and release of prostaglandins, bradykinin and pain-causing substances, thereby achieving the purpose of relieving pain. In addition, intracavitary injection of ozone could directly act on nerve

Table 4. Univariate analysis table

	Poor Prognosis Group (n=26)	Good Prognosis Group (n=106)	X^2/t	P
Gender			0.187	0.666
Male	13 (50.00)	48 (45.28)		
Female	13 (50.00)	58 (54.72)		
Age (Years)	70.31±4.91	61.21±5.75	7.427	<0.001
Disease Duration (Months)	21.58±7.11	18.49±6.95	2.023	0.045
BMI (Kg/m^2)	24.42±3.69	25.10±2.98	0.993	0.323
Disease Site			1.724	0.189
Unilateral Disease	16 (61.54)	50 (47.17)		
Bilateral Disease	10 (38.46)	56 (52.83)		
X-Ray Kellgren-Lawrence Grading			4.433	0.109
I	4 (15.38)	37 (34.91)		
II	10 (38.46)	38 (35.85)		
III	12 (46.15)	31 (29.24)		
Family History of Knee Arthritis			2.887	0.089
Yes	11 (42.31)	27 (25.47)		
No	15 (57.69)	79 (74.53)		
Smoking			1.056	0.304
Yes	5 (19.23)	31 (29.25)		
No	21 (80.77)	75 (70.75)		
Heavy Manual Labor Occupation			0.536	0.464
Yes	9 (34.62)	29 (27.36)		
No	17 (65.38)	77 (72.64)		
Post-Treatment WOMC Score	43.23±6.87	37.53±10.37	3.137	0.002
Post-Treatment VAS Score	3.35±1.20	2.34±1.15	3.979	<0.001
Post-Treatment Oc (Ug/L)	5.39±1.39	6.03±1.12	2.485	0.014
Post-Treatment Opg (Pg/Ml)	4.03±1.10	4.61±1.15	2.324	0.022
Post-Treatment Rankl (Pg/Ml)	26.40±4.39	23.73±4.14	2.912	0.004
Post-Treatment Il-1β (Pg/Ml)	31.31±8.00	27.44±7.68	2.284	0.024
Post-Treatment Il-6 (Pg/Ml)	25.28±6.44	21.28±7.6	2.473	0.015
Post-Treatment Tnf-α (Pg/Ml)	38.27±10.55	32.93±10.41	2.338	0.021
Treatment Method			6.442	0.011
Arthroscopic Irrigation Alone	18 (69.23)	44 (41.51)		
Arthroscopic Irrigation Combined with Ozone Injection	8 (30.77)	62 (58.49)		

BMI: Body Mass Index; WOMAC: Western Ontario McMaster; VAS: Visual Analogue Scale; OC: Osteocalcin; OPG: Osteoprotegerin; RANKL: Nuclear Transcription Factor KB Receptor Activator Ligand.

Table 5. Multivariate analysis table

Factor	B	S.E.	Wals	Sig.	Exp (B)	95% CI of Exp (B)	
						Lower Limit	Upper Limit
Age	0.580	0.144	16.185	0.001	1.786	1.347	2.370
Disease Course	0.124	0.062	3.972	0.046	1.132	1.002	1.279
VAS Score After Treatment	0.840	0.385	4.754	0.029	2.316	1.089	4.925
Il-6 After Treatment	0.170	0.078	4.722	0.030	1.186	1.017	1.382

endings and stimulate inhibitory interneurons to release enkephalin and other substances, thereby achieving an analgesic effect [21]. Wang et al. [22] collected the medical records

of 80 KOA patients with Kellgren-Lawrence grade II or III, all of whom underwent arthroscopic surgery and found that those who received ozone injection after surgery had less pain and improved joint function, as well as better quality of life than those who didn't, which is also similar to our conclusion. In the study of Fakhari et al. [23], the efficacy of low-level laser therapy and intra-articular ozone injection in KOA was compared, and it was found that ozone injection had better effect on improving joint function of patients than low-level laser therapy, and was more suitable for patients cannot bearing surgical intervention. In the study of Babaei-Ghazani et al. [24], the abilities of ozone injection and corticosteroid injection to improve KOA were compared, and it was found that the joint effusion of patients treated with ozone was significantly reduced, and the action lasted significantly longer than that of corticosteroid injection. This also suggested that combined ozone therapy could provide better results.

Osteogenesis-osteoclast imbalance is considered to be an essential cause of local bone destruction and systemic bone loss in KOA joints, mainly manifested as bone remodeling, abnormal activation of osteoclasts, bone resorption and bone formation imbalance, which in turn lead to peripheral bone loss and abnormal changes in serum bone metabolism index levels [25]. OC, a non-collagen molecule synthesized and secreted by osteoblasts, is involved in the mineralization and formation of bone. OPG can inhibit the differentiation and maturation of osteoclasts, thereby inhibiting bone resorption [26]. In our study, OC, OPG, and RANKL in both groups after treatment were better than before treatment, and the OC and OPG in the Observation Group after treatment were higher than those of the Control Group, while its RANKL was comparatively lower. This suggests that arthroscopic debridement combined with ozone therapy was more conducive to restoration of bone metabolism, thereby promoting the recovery of bone and joint function. The study of Sunarso et al. [27] found that ozone could promote the proliferation and differentiation of MSCs derived from rat bone marrow and improve bone metabolism indexes.

The occurrence of KOA is mainly caused by joint degeneration or a metabolic disorder, and immune and inflammatory factors also play a key role in its occurrence and development. As a pro-inflammatory cytokine, TNF-α can stimulate the activity of osteoclasts and inhibit the activity of osteocytes. It can also activate IL-6, which inhibits the synthesis of proteoglycans and cartilage collagen and participate in the occurrence and development of KOA [28]. IL-1β is a hormone-like polypeptide inflammatory factor that also plays an important role in chondrocyte apoptosis [29]. In this study, the serum levels of IL-1β, TNF-α, and IL-6 in both groups before surgery were all at high levels, yet were all decreased markedly after treatment, and those of the Observation Group were significantly lower than in the Control Group. This suggests that arthroscopic debridement could remove the inflammatory factors to some extent, and combined ozone intra-articular injection could further control the inflammatory response. Meanwhile, inflammatory factors such as TNF-alpha action could further control the inflammatory response. Certainly, while elimination of inflammation can reduce the pain of patients. Fortunately, low concentration of medical ozone can reduce the level of serum inflammatory factors in patients with lumbar disc herniation with its analgesic and anti-inflammatory effects; while high concentrations of medical ozone will increase serum inflammation levels, as well as patient pain and discomfort [30]. We also explored the independent risk factors affecting the prognosis of patients, and found that higher age, longer course of disease, higher VAS score after treatment, and higher IL-6 level after treatment were independent risk factors for poor prognosis.

This study has some shortcomings. First, studies with extended observation time and long-term treatment effect are needed to provide more objective data. Second, the pathologic Kellgren-Lawrence grades included in this study did not exceed grade III, so the effect of combination therapy with ozone on more severe patients remains unclear. Finally, animal experiments are needed for further understanding of the specific mechanism.

In conclusion, joint irrigation combined with ozone injection therapy had a good effect in KOA, and could effectively relieve the clinical symptoms and symptom levels of patients, improve their bone metabolism indexes, and contribute to recovery of knee joint function.

Disclosure of conflict of interest

None.

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