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Comparison of the effects of intra-articular injection of ozone and sodium hyaluronate in the treatment of knee osteoarthritis on pain and knee joint function

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ABSTRACT

Objective: To compare the effects of intra-articular injection of ozone and sodium hyaluronate in the treatment of knee osteoarthritis on pain and knee joint function.

Methods: A total of 90 patients with knee osteoarthritis admitted to our hospital from April 2018 to April 2020 were divided into the ozone group and the sodium hyaluronate group according to the random number table, with 45 cases in each group. The ozone group was treated with intra-articular ozone injection, and the sodium hyaluronate group was treated with intra-articular injection of sodium hyaluronate, both once a week for 5 weeks. The serum MMP-3, IL-1β, TGF-β levels before treatment, 5 weeks of treatment, pain VAS score, knee HSS score and adverse reactions of the two groups before treatment, 5 weeks of treatment, and 3 months after treatment were compared between two groups.

Results: The serum MMP-3 and IL-1β of the two groups were lower than before treatment, and serum TGF-β was higher than before treatment for 5 weeks (P<0.05). There was no significant difference in serum MMP-3, IL-1β and TGF-β between the ozone group and the sodium hyaluronate group after treatment (P>0.05). The pain VAS scores of the two groups of patients after treatment for 5 weeks and 3 months after treatment were significantly higher than those before treatment (P<0.05). There was no significant difference in pain VAS scores between the ozone group and the sodium hyaluronate group before treatment and 3 months after treatment (P>0.05). The pain VAS score of the ozone group after 5 weeks of treatment was lower than that of sodium hyaluronate Group (P<0.05). The HSS scores of the two groups of patients treated for 5 weeks and 3 months after treatment were significantly higher than before treatment (P<0.05). There was no significant difference between the HSS scores of the ozone group and the sodium hyaluronate group before treatment and 5 weeks of treatment (P>0.05). The HSS score of the sodium hyaluronate group was higher than that of the ozone group at 3 months after treatment (P <0.05). 46.67% of the patients in the ozone group experienced local soreness during the injection, which was significantly higher than 8.89% in the sodium hyaluronate group (P<0.05). 6.67% of patients in the ozone group had a transient heart rate drop, while the sodium hyaluronate group did not. The incidence of swelling and chills was lower in the two groups, and the difference was not statistically significant (P>0.05).

Conclusion: Intra-articular injection of ozone and sodium hyaluronate can effectively inhibit knee joint inflammation. The short-term effect of ozone is better, and the analgesic effect is more obvious; the long-term effect of sodium hyaluronate is more ideal, and the knee joint function is improved, and safer.

Keywords: Knee osteoarthritis; pain; knee joint function; intra-articular injection; ozone; sodium hyaluronate

Introduction

The incidence rate of osteoarthritis which has increased with age, has reached 10% in the world under the age of 60 and knee osteoarthritis has

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become one of the major causes of disability in the elderly (Chen and Shi, 2018). Surgical operation and conservative drug treatment are the main treatment methods of knee osteoarthritis, and the latter one is more widely accepted by most patients. Drug treatment includes oral administration and intra-articular injection. Generally, oral administration can cause gastrointestinal reactions, bone necrosis, obesity and other side effects. And intra articular injection of drugs whose the efficacy was recognized, can directly deliver drugs to the diseased joints, which has a direct effect of in situ treatment and also the initial concentration of target joints is high with the reduced side effects (Zhou and Wang, 2020). Above all, 90 patients with knee osteoarthritis were selected as examples to compare the therapeutic effect of intra-articular injection of ozone and sodium hyaluronate in this study.

1. Material and methods

1.1 Clinical data

90 patients with knee osteoarthritis in our hospital from April 2018 to April 2020 were selected as the research objects, and the research was approved by the hospital ethics committee. They were randomly divided into ozone group and sodium hyaluronate group, 45 cases in each group.; In ozone group, there were 25 males and 20 females with an average age of 58.78 ± 6.12 years (range from 44 to76 years old); the course of disease was 2.23 ± 0.61 years (range from 1 to4 years); K-L classification includes 12 cases of grade I, 20 cases of grade II and 13 cases of grade III. In the sodium hyaluronate group, there were 28 males and 17 females with an average age of 58.31±6.73 years (range from 42 to 78 years old); the course of disease was 2.38 ± 0.72 years (range from 1 to 5 years); K-L classification includes 14 cases in grade I, 19 cases in grade II and 12 cases in grade III. There was no significant difference in baseline data between the two groups ($P > 0.05$).

Inclusion criteria: (1) age > 18 years old. (2) X-ray showed that Kellgren's K-L grade was score at Ⅰ～Ⅲ level in knee osteoarthritis. (3) There was no treatment history within 4 weeks. (4) The strength line of limbs is normal. (5) Informed consent forms were signed

Exclusion criteria: (1) patients with gout, knee tuberculosis, rheumatoid arthritis, knee deformity. (2) Patients with diabetes, hypertension, arrhythmia and other basic diseases. (3) Pus cells were found in synovial fluid test. (4) Patients who had a history of severe infection of the whole body or knee joint within one month before our enrollment. (5) Patients with cognitive impairment or mental illness. (6) Patients with allergic to treatment drugs.

1.2 Treatment

The knee joint was injected in the sitting position. The affected knee joint was flexed 90 ° during the treatment. The lateral knee eye was taken as the puncture point. After local anesthesia and routine disinfection cloth, the needle was injected with 5 ml disposable syringe. After the puncture reached the joint cavity, the ozone group was slowly injected with 25 μg/ml ozone 5 ml (ozon2000 ozone treatment instrument, Germany Zotzmann); the sodium hyaluronate group was slowly injected with sodium hyaluronate 2 ml (Shandong boshilun Freida pharmaceutical, No. 20160104). After injection, the knee joint was slightly flexed and extended for 10 times to fully distribute the liquid on the surface of cartilage and synovium. Two groups of patients were treated once a week with a total of 5 times.

1.3 observation index

1.3.1 Serological test

Pre-treatment and 5 weeks after treatment, 3 ml fasting peripheral venous blood was collected and centrifuged for 15 min at the speed of 3000 r/min. The serum levels of MMP-3, IL-1β and TGF-β were measured by ELISA.

1.3.2 Degree of pain

Visual analogue scale (VAS) was used to evaluate (Lu et al., 2018): 0-3 points were mild pain, 4-6 points were moderate pain, 7-10 points were severe pain. VAS scores of pains before treatment, 5 weeks of treatment and 3 months after treatment were recorded

1.3.3 knee function

The knee HSS score (Qian et al., 2019) was used to evaluate the knee joint function of the two groups: six dimensions of function, pain, stability, range of motion, knee flexion deformity and score reduction items. The total score was 100 points, > 85 points was excellent, 70-84 points was good, 60-69 points was medium, and < 60 points was poor.

1.3.4 adverse reactions

The adverse reactions of the two groups were recorded, including acid swelling, heart rate drop, swelling, chills, etc during the injection or after

injection.

1.4 statistical methods

SPSS19.0 was used for statistical analysis. In enumeration data (%) statistical analysis, it was analyzed by χ^2 test or continuous correction χ^2 test for comparison. In measurement data ($\bar{x} \pm s$), multiple time points within the group comparison were analyzed by repeated measurement analysis of variance and pairwise comparison was conducted by LSD-t test. The difference was statistically significant when *P* value < 0.05.

2 Results

2.1 Serological indicators

The levels of MMP-3 and IL-1 β in the two groups after 5 weeks of treatment were lower than those before treatment, and the serum TGF - β was higher than that before treatment (*P* < 0.05). There was no significant difference in serum MMP-3, IL-1 β and TGF - β between ozone group and sodium hyaluronate group after treatment (P > 0.05). See Table 1.

Table 1. **Comparison of serological indexes between the two groups ($\bar{x} \pm s$)**

Group	Number	MMP-3（ng/L）		IL-1β（pg/mL）		TGF-β（ng/mL）	
		Pre-treatment	5 weeks after treatment	Pre-treatment	5 weeks after treatment	Pre-treatment	5 weeks after treatment
Ozone group	45	4.25±0.83	3.21±0.44*	3.95±0.63	2.67±0.41*	1.02±0.31	1.62±0.41*
Sodium hyaluronate group	45	4.19±0.77	3.30±0.48*	3.88±0.59	2.76±0.43*	1.04±0.28	1.59±0.44*
t value		0.356	0.927	0.544	1.016	0.321	0.335
P value		0.723	0.356	0.588	0.312	0.749	0.739

Note: compared with before treatment, * P < 0.05

2.2 Degree of pain

The VAS scores of pains in 5 weeks and 3 months after treatment were significantly higher than those before treatment (*P*<0.05). There was no significant difference in VAS score between ozone group and sodium hyaluronate group before and 3 months after treatment (*P*>0.05). The VAS score of pain in ozone group was lower than that in sodium hyaluronate group after 5 weeks of treatment (P < 0.05). See Table 2.

Table 2. **Comparison of VAS scores in two groups (score, $\bar{x} \pm s$)**

Group	Number	Pre-treatment	5 weeks after treatment	3 months after treatment	*F* value	*P* value
Ozone group	45	6.89±1.32	3.86±0.76*	3.48±0.56*	164.928	0.000
Sodium hyaluronate group	45	7.04±1.54	4.22±0.81*	3.50±0.62*	140.394	0.000
t value		0.496	2.174	1.766		
P value		0.621	0.032	0.081		

Note: compared with before treatment, *P<0.05

2.3 knee joint function

The HSS scores of the two groups at 5 weeks and 3 months after treatment were significantly higher than those before treatment (*P*<0.05). There was no significant difference in HSS score between ozone group and sodium hyaluronate group before and after 5 weeks of treatment (*P*>0.05). The HSS score of sodium hyaluronate group was higher than that of ozone group 3 months after treatment (*P*<0.05). See Table 3.

Table 3. **Comparison of HSS score of knee joint between two groups (score, $\bar{x} \pm s$)**

Group	**Number**	**Pre-treatment**	**5 weeks after treatment**	**3 months after treatment**	***F* value**	***P* value**
Ozone group	45	63.26±7.78	73.46±8.33*	83.76±7.89*	73.808	0.000
Sodium hyaluronate group	45	62.69±7.95	71.38±7.58*	78.13±8.55*	41.743	0.000
t value		0.344	1.239	2.093		
P value		0.732	0.219	0.039		

Note: compared with before treatment, *P<0.05

2.4 Adverse reactions

46.67% of patients in ozone group had local acid swelling during injection, which was significantly higher than 8.89% in sodium hyaluronate group (P<0.05). 6.67% of the patients in the ozone group had transient heart rate decrease, but not in the sodium hyaluronate group. The incidence of swelling and chilliness in the two groups were lower, and the difference was not statistically significant (P>0.05). See Table 4.

Table 4. **Comparison of adverse reactions between the two groups (cases, %)**

Group	Number	Acid distension	Decreased heart rate	Swelling	Chilly
Ozone group	45	21（46.67）	3（6.67）	2（4.44）	1（2.22）
Sodium hyaluronate group	45	4（8.89）	0	4（8.89）	3（6.67）
χ^2 value		16.006	1.379*	0.179*	0.262*
P value		0.000	0.240	0.673	0.609

Note: * means continuous correction χ^2 test

3 Discussion

Knee osteoarthritis is more common in middle-aged and elderly people, especially in obese women. The etiology is complex, and it is related to trauma, inflammation and joint strength line (Wang et al., 2019). The study found that (Liao et al., 2020), the disease not only damages the articular cartilage, but also affects the whole joint. The conservative treatment aims at relieving symptoms, improving joint function, delaying the progress of the disease, and creating favorable conditions for the repair of the injured joint. Intra articular injection of drugs can directly deliver drugs to the diseased joints, eliminate inflammation, block the progress of pathological reflex, eliminate inflammatory exudative swelling, improve local blood circulation, so as to relieve pain symptoms, and become one of the main treatment methods of the disease (KUMARA et al., 2017).

In this study, intra-articular injection of ozone and sodium hyaluronate were used to treat patients with knee osteoarthritis. The results showed that the levels of serum inflammatory factors decreased significantly and TGF-β increased significantly in the two groups after treatment, but the change range was the same, there was no significant difference, suggesting that intra-articular injection of ozone and sodium hyaluronate can effectively inhibit inflammation. It has been proved that ozone can kill almost all bacteria, viruses, fungi, etc. The possible mechanism of ozone treatment for patients with knee osteoarthritis maybe(Li et al., 2020; Zhang et al., 2020): 1. local injection of ozone can effectively neutralize various reactive oxides produced by inflammatory reaction, and can antagonize the inflammatory reaction by inhibiting the synthesis of prostaglandin; 2. it can inhibit the sensory fibers of pulpless injury, stimulate the inhibitory intermediate neurons and increase the release of enkephalin; 3. It can block the vicious cycle of articular cartilage injury, maintain the structure and function of cartilage cell membrane, promote normal proliferation of chondrocytes and synthesis of cartilage matrix, protect articular cartilage and delay joint degeneration. Sodium hyaluronate is one of the components of joint fluid and cartilage matrix, which can lubricate joint cavity, reduce tissue friction, and buffer the stress of articular cartilage. Some studies (Chen et al., 2019; Meng and Su, 2018) have pointed out that the degeneration of cartilage and synovium and the decrease of hyaluronic acid in synovial fluid with age are one of the causes of joint pain. Intra articular injection of high molecular weight and high concentration of sodium hyaluronate can not only effectively inhibit the inflammatory reaction of synovial tissue, but also increase the content of sodium hyaluronate, strengthen the lubricating effect of joint fluid, protect and repair the damaged cartilage, which is conducive to the healing and regeneration of articular cartilage, so as to improve the knee joint function of patients. The study found that (Yan et al., 2018; Tang et al., 2018), after intra-articular injection of sodium hyaluronate, it entered the synovium, cartilage surface and adjacent muscle tissue and muscle space, reaching the peak value. At the same time, it prevented the invasion of toxin and immune complex through the protective effect of barrier, so as to promote the decline of swelling, and thus the vicious circle of joint injury.

However, there were some differences in analgesia and improvement of knee joint function between the two treatments. The VAS scores of pains in the two groups both were decreased after intra-articular injection. The VAS score of pain after 5 weeks of ozone injection was lower than that of sodium hyaluronate group, suggesting that

ozone has better effect on pain inhibition. In recent years, medical ozone injection is a new method for the treatment of tissue edema. Studies have found that (MAUDENSP et al., 2018; JONESIA et al., 2019) ozone is a strong oxidant, second only to fluorine. It has the advantages of rapid pain relief in the

treatment of aseptic inflammation, and can promote the dissipation of edema and reduce local temperature. Also, after decomposition into more stable oxygen, it will not cause secondary pollution and sustained organ tissue damage. With good tissue dispersion, it can play an exact role in a large range, and has been widely used in various kinds of painful diseases with significant analgesic effect. However, the effect of sodium hyaluronate is relatively gentle, so there are major differences in analgesic effect. The knee joint function in the sodium hyaluronate group was better than that in the ozone group three months after treatment, suggesting that the long-term effect of intra-articular injection of sodium hyaluronate is better, which is related to the poor stability of ozone. According to foreign studies (TANAKAT et al., 2019; SARKARA et al., 2019), the retention time of drugs in synovial joints after intra-articular injection will affect the therapeutic effect. The half-life of ozone at room temperature is only 20 min. After being injected into the joint cavity, the degradation reaction and absorption speed in human body are also faster, so higher drug concentration can be obtained, but the duration of efficacy is relatively short, and the long-term effect is not as expected (DUYMUSTM et al., 2017; GOTON et al., 2017). However, the local degradation of sodium hyaluronate is slow after intra-articular injection, which can delay cartilage degeneration. This is the main reason why the knee joint function of sodium hyaluronate group is better than that of ozone group 3 months after treatment.

In addition, there were significant differences in adverse reactions between the two groups. Ozone group would cause local acid distension and discomfort due to strong irritation during injection. In addition, ozone can cause the heart rate of individual patients to drop to 50 beats/ min, but sodium hyaluronate does not appear. At present, the safety of ozone has been widely recognized. Although the incidence of central rate decline in this study is not frequent, it still should be paid attention to. It has also been reported in foreign countries (RUDRIKJI et al., 2019) that acute inferior myocardial infarction occurs in patients with no cardiovascular history. Ozone treatment is not completely without risk, and it needs to be vigilant in practic.

In conclusion, intra-articular injection of ozone and sodium hyaluronate can effectively inhibit knee joint inflammation, protect and repair damaged cartilage. Among them, the analgesic effect of ozone is more obvious, the short-term effect is better; and the long-term effect of sodium hyaluronate is more ideal, which is conducive to the improvement of knee joint function, and has higher safety.

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