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# Effect of Sodium Hyaluronate and Betamethasone Injection in Knuckle Articular Cavity on Serum Inflammatory Factors and Metalloproteinase of Knee Osteoarthritis Patients

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## ABSTRACT

The aim of this study was to observe the efficacy of injection of sodium hyaluronate combined with betamethasone into knuckle articular cavity in knee osteoarthritis treatment, and to analyze its effect on the prognosis of knee joint function. A total of 120 knee osteoarthritis patients admitted to our hospital from January 2019 to February 2020 were selected as the study subjects and randomly divided into control group and observation group (60 cases each). The control group was given injection of sodium hyaluronate in knuckle articular cavity, and the observation group was further treated with compound betamethasone. Clinical efficacy of the two groups was observed after treatment, the knee joint pain before and after treatment was evaluated using visual analogue scale (VAS), and Lysholm knee function score was given. The patients' serum interleukin-1β (IL-β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were detected using ELISA method before treatment and 3 months after treatment; incidence of adverse prognostic reactions was compared between the two groups. After treatment, the observation group had 34 markedly effective cases and 21 effective cases, with total effective rate of treatment at 91.67%. The figure was significantly higher compared to 80.00% of the control group, showing statistically significant difference ($P$<0.05). After treatment, the patients' VAS score and 20 m walking time were significantly reduced, with Lysholm score increased significantly ($P$<0.05). The observation group patients' VAS, Lysholm knee score and 20 m walking time were 3.42±0.60 points, 87.74±10.36 points and 7.16±2.05 s, respectively, which were significantly superior to the control group, showing statistically significant difference ($P$<0.05). After treatment, the patients' inflammatory factor level was significantly lower, and matrix metalloproteinases content was also significantly reduced ($P$<0.05). IL-1β, IL-6 and TNF-α in the observation group were respectively 8.07±3.13 ng/mL, 9.31±6.83 ng/mL and 7.72±1.86 pg/mL, with MMP-3 and MMP-9 contents at 29.42±6.74 and 20.23±5.24, showing significantly superior improvement compared with the control group and indicating statistically significant difference ($P$<0.05). The incidence of adverse reactions was 3.33% (2/60) in the observation group, which was significantly lower than 15.00% in the control group, and the difference was not statistically significant ($P$<0.05). To conclude, significant therapeutic effect was observed in KOA patients treated with injection of sodium hyaluronate combined with compound betamethasone in knuckle articular cavity, which can effectively relieve pain and reduce serum inflammatory factors IL-1β, IL-6, TNF-α and matrix metalloproteinase MMP-3, MMP-9 contents, relieve knee arthritic excessive activation and protease degradation, reduce the incidence of adverse reactions, and promote the recovery of prognostic joint function.

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**Authors' Contribution**
**ZJW put forward the clinical efficacy of the two groups after treatment. Y Z analyzed the clinically delayed disease progression. XHS helped with the joint function recovery. All authors discussed the results and wrote the manuscript.**

**Key words**
**Sodium hyaluronate, Compound betamethasone, Injection in knuckle articular cavity, Knee osteoarthritis**

## INTRODUCTION

Knee osteoarthritis (KOA) is a joint degenerative orthopedic disease, whose pathological features include secondary hyperostosis, synovial membrane or joint capsule disease, and inflammatory cell infiltration in joint tissues. Patients' main clinical symptoms include knee joint pain and prognostic dysfunction (Zhao *et al*., 2019; Liu, 2018). KOA has a higher incidence in the elderly, and the prognosis is poor. In severe cases, knee joint flexion deformity and walking obstacles may even occur (Luo *et al*., 2019). Clinically, KOA treatment is mainly to ease pain, resist inflammation, delay disease progression, promote prognosis, and improve patients' quality of life. Sodium hyaluronate as an important component of joint synovial fluid is often adopted to clinically treat KOA

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via injection in knuckle articular cavity. As the preferred treatment option, it can effectively reduce the release of inflammatory mediators in synovial tissue, protect the articular cartilage environment, and promote tissue healing and regeneration (Jiang *et al*., 2020). Studies have reported that although sodium hyaluronate alone receives acceptable efficacy in the treatment of knee osteoarthritis, there are still some patients with unsatisfactory prognosis (Kou *et al*., 2020). Compound betamethasone injection, a new generation of glucocorticoid preparations with more applications in recent years, can inhibit the immune inflammatory response caused by excessive activation of glucocorticoids, reduce inflammatory cascade caused by immune imbalance of joint injury, and reduce the damage of inflammatory mediators on articular cavity osteocytes, thereby playing a therapeutic role (Hu, 2000; Zhang *et al*., 2018a). However, how about the efficacy of combined injection of sodium hyaluronate and compound betamethasone in knuckle articular cavity in KOA treatment? There are no detailed reports on the prognostic inflammatory factors and the recovery of knee joint function. This paper aims to investigate the effect of combined treatment on serum inflammatory factors, MMP-3, MMP-9 and joint function prognosis of KOA patients.

## MATERIALS AND METHODS

*Clinical data*

A total of 120 knee osteoarthritis patients admitted to our hospital from January 2019 to February 2020 were selected as the study subjects.

Inclusion criteria: (1) Those who meet the diagnostic criteria of knee osteoarthritis established by the tenth edition of "Surgery" and are definitely diagnosed; (2) Those who have osseous enlargement, knee joint pain and walking difficulty in the past six months; (3) Those with unilateral knee joint disease; (4) Those who have not received knee surgery or local treatment in the past 3 months.

Exclusion criteria: (1) Knee fractures, obvious swelling and effusion, deformities, or with previous joint replacement surgery in the lower limb; (2) Complicated with other malignant tumors, liver and kidney insufficiency or immune diseases; (3) Arthritis caused by other pathogenesis, like metabolic arthritis or rheumatism; (4) Those who have mental illness and cannot cooperate with treatment. The study was approved by the medical ethics committee of the hospital, and the patients and their families signed the informed consent form.

In this research, 120 KOA patients were randomly divided into control group and observation group (60 cases each). In the control group, there were 34 males and 26 females; aged 44~75 years, the patients had an average age of 60.36±6.22 years; with 1~year' course of disease, the patients had an average course of 2.45±1.06 years. In the observation group, there were 35 males and 25 females; aged 45~72 years, the patients had an average age of 60.74±5.65 years; with 1~year' course of disease, the patients had an average course of 2.48±1.45 years. There were no statistically significant differences in general information such as gender ratio, age and disease course between the two groups ($P$>0.05), showing comparability.

*Treatment methods*

The control group was given injection of sodium hyaluronate in knuckle articular cavity. The patient took a supine position, flexed the affected side with 90° knee flexion; 2% lidocaine hydrochloride injection (2 mL) was injected for local anesthesia, then local puncture was performed, followed by pumpback when emptiness was felt. Infuse 25 mg sodium hyaluronate injection (specification: 2 mL/20 mg, Shandong Bausch and Lomb Freda Pharmaceutical Co., Ltd., batch number P201781142525669) when there is no blood return. Ensure that sodium hyaluronate is evenly distributed on the surface of articular cartilage and synovial membrane. Treatment time: 1 time/week, 4 times/course for 3 continuous courses.

The observation group was treated with compound betamethasone injection (Chongqing Huapont Pharm Co., Ltd., batch number 20183412) on the basis of the control group. The usage and dosage of sodium hyaluronate injection was the same as that of the control group. Then, in the first course of treatment, 1 mL of compound betamethasone injection was injected in the knuckle articular cavity, and during the second and third treatment courses, 2 mL of compound betamethasone injection was injected in the knuckle articular cavity. The treatment cycle was the same as that of the control group. During the treatment, attention was paid to bed rest and avoiding weight-bearing activities (Liu *et al*., 2019).

*Observation indicators*

For evaluation of clinical efficacy, if knee joint symptoms such as pain, swelling, etc. disappear, knee joint activity is not restricted, function is normal without affecting life and work, the treatment is markedly effective. If knee joint symptoms such as pain, swelling, etc. are improved than before, knee joint activity is limited to a certain extent, the joint function is improved, but with certain impact on life and work, the treatment is effective. If symptoms, signs, joint function, etc. have no obvious improvement, or even aggravate, then treatment is

ineffective. KOA treatment efficacy = number of (markedly effective + effective) cases/total number of cases × 100%.

Knee joint pain and knee joint function were compared between the two groups before and after treatment. Patients' pain was assessed using visual analogue scale (VAS). VAS has a full score of 10 points, no pain is scored 0, and severe totally unbearable pain is scored 10 points. A lower score indicates lighter pain. In terms of Lysholm knee joint function scoring: The Lysholm knee joint scoring system includes the following aspects: pain, restlessness, atresia, swelling, degree of claudication, stair climbing, squatting, upholder use, etc., with a full score of 100 points. A higher score indicates better recovery of knee joint function and better knee joint function. At the same time, the patients' 20 m walking time was recorded before and after treatment.

Before and after treatment, 4 mL of venous blood was drawn from the patient with empty stomach, centrifuged at 3000 rpm in for 10 min. The supernatant was taken and stored in -20°C refrigerator for later use. Using enzyme-linked immunosorbent assay ELISA, the serum levels of inflammatory factors IL-1β, IL-6, TNF-α and matrix metalloproteinase MMP-3 and MMP-9 were determined according to the instructions. The kit was provided by Nanjing Jiancheng Bioengineering Institute.

The patients were followed up for another 3 months after treatment, and incidence of adverse prognostic reactions was recorded for the two groups.

*Statistical analysis*

SPSS21.0 was used to statistically analyze the data. The measurement data results conforming to normal distribution include VAS, Lysholm score, 20 m walking time, disappearance time of knee joint effusion, inflammatory factors IL-1β, IL-6, TNF-α and matrix metalloproteinases MMP-3, MMP-9 levels, which were indicated by ($\bar{x}\pm s$). Independent sample t test was used for comparison between groups. The count data including clinical efficacy and incidence of adverse reactions were indicated by the number of cases/percentage (%), and $\chi^2$ test was used for comparison between groups. $P<0.05$ indicates statistically significant difference.

## RESULTS

*Evaluation of clinical efficacy*

After treatment, the observation group had 34 markedly effective cases and 21 effective cases, with total effective rate of treatment at 91.67%. The figure was significantly higher compared to 80.00% of the control group, showing statistically significant difference ($P<0.05$) (Table I).

**Table I. Comparison of clinical efficacy between the two groups.**

| Classification | Control group | Observation group | $\chi^2$ | P |
|---|---|---|---|---|
| markedly effective | 20 | 34 | 7.512 | 0.023 |
| effective | 28 | 21 | | |
| ineffective | 12 | 5 | | |
| total effective rate | 80.00% (48/60) | 91.67% (55/60) | | |

*VAS, Lysholm knee joint score and 20 m walking time*

Before treatment, there was no significant difference in VAS, Lysholm knee score and 20 m walking time between the two groups (P>0.05). After treatment, the patient's VAS score and 20 m walking time were significantly reduced, while Lysholm score was increased significantly (P<0.05). The observation group patients' VAS, Lysholm knee score and 20 m walking time were respectively 3.42±0.60 points, 87.74±10.36 points and 7.16±2.05 s, which were significantly superior to the control group, showing statistically significant difference (P<0.05) (Table II).

**Table II. Comparison of VAS, Lysholm knee joint score and 20 m walking time between the two groups before and after treatment ($\bar{x}\pm s$).**

| Classification | | Control group | Observation group | t | P |
|---|---|---|---|---|---|
| VAS/ point | Before treatment | 6.41±0.76 | 6.40±1.00 | 0.027 | 0.979 |
| | After treatment | 6.40±0.73* | 3.42±0.60* | 5.505 | <0.001 |
| Lysholm score/ point | Before treatment | 54.28±8.47 | 55.23±9.71 | -0.476 | 0.635 |
| | After treatment | 76.15±7.93* | 87.74±10.36* | -5.636 | <0.001 |
| 20 m walking time/s | Before treatment | 16.21±3.11 | 15.84±3.45 | 0.12 | 0.884 |
| | After treatment | 9.22±2.14* | 7.16±2.05* | 4.024 | 0.002 |

Note: After treatment, *$P<0.05$.

*Inflammatory factors and matrix metalloproteinases levels*

Before treatment, there was no significant difference in inflammatory factors and matrix metalloproteinases between the two groups ($P>0.05$). After treatment, the patients' inflammatory factor level was significantly lower and matrix metalloproteinases content was also significantly reduced ($P<0.05$). IL-1β, IL-6 and TNF-α in

the observation group were respectively 8.07±3.13 ng/mL, 9.31±6.83 ng/mL and 7.72±1.86 pg/mL, with MMP-3 and MMP-9 contents at 29.42±6.74 and 20.23±5.24, showing significantly superior improvement compared with the control group and indicating statistically significant difference ($P$<0.05) (Table III).

**Table III. Comparison of inflammatory factor and metalloproteinases levels between the two groups before and after treatment ($\bar{x}$±$s$).**

| Classification | | Control group | Observation group | t | P |
|---|---|---|---|---|---|
| IL-1β (ng/mL) | Before treatment | 26.13±7.13 | 25.97±6.33 | 0.103 | 0.905 |
| | After treatment | 10.48±4.24* | 8.07±3.13* | 5.024 | <0.001 |
| IL-6 (ng/mL) | Before treatment | 38.12±10.06 | 38.28±9.86 | -0.234 | 0.873 |
| | After treatment | 13.65±7.62* | 9.31±6.83* | 4.754 | <0.001 |
| TNF-α (pg/mL) | Before treatment | 14.37±2.84 | 14.62±2.15 | -0.067 | 0.944 |
| | After treatment | 10.14±2.08* | 7.72±1.86* | 6.232 | <0.001 |
| MMP-3 (ng/mL) | Before treatment | 93.26±14.24 | 92.64±14.34 | 0.082 | 0.924 |
| | After treatment | 40.82±7.82* | 29.42±6.74* | 8.342 | <0.001 |
| MMP-9(ng/mL) | Before treatment | 58.74±8.42 | 59.03±7.42 | -0.234 | 0.873 |
| | After treatment | 33.23±7.04* | 20.23±5.24* | 7.242 | <0.001 |

Note: After treatment, *$P$<0.05.

*Comparison of adverse reactions between the two groups after treatment*

Two patients in the observation group had transient pain and swelling in the knee joint, while 4 patients in the control group had transient pain and swelling in the knee joint, plus 2 cases of low fever and 3 cases of rash. The incidence of adverse reactions in the observation group was 3.33% (2/60), which was significantly lower than 15.00% in the control group, and the difference was not statistically significant ($\chi^2$=4.904, $P$=0.027).

## DISCUSSION

Knee osteoarthritis occurs frequently in elderly patients. As a chronic disease characterized by pathological changes such as articular cartilage destruction, cartilage bone sclerosis, and marginal chondrogenesis, it features progressive development and gradual aggravation. Without timely treatment, it will cause joint stiffness, limited mobility, walking difficulty, and even deformities and disabilities (Yan *et al*., 2020; Si *et al*., 2019). At present, the treatment of knee osteoarthritis includes surgery, medicine, and traditional Chinese medicine, which is to correct joint deformities, relieve pain, and help joint function recovery. Injection in knuckle articular cavity is commonly used in KOA treatment, which can directly act on the articular surface to inhibit inflammation and promote the healing of knee joint tissue. Sodium hyaluronate is a kind of lubricating fluid, which can help KOA patients lubricate and repair the knee joint tissue after injection in knuckle articular cavity. The main mechanism is that sodium hyaluronate enters the knee joint cavity and binds to glycoproteins, acts on the cartilage surface, lubricates the tissue while reducing pain and repairs joint damage. In addition, it can also inhibit endotoxin damage to the joints and alleviate the progression and deterioration of degenerative diseases (Bannuru *et al*., 2019; Lajeunesse *et al*., 2003).

Compound betamethasone is commonly used in the treatment of orthopedic joint diseases. Betamethasone dipropionate, as one of the glucocorticoid inhibitors, is slightly soluble, slow in absorption, and has a long duration of efficacy. It can prolong the drug action time in KOA treatment, avoid inflammation and excessive immune response activation caused by excessive hormone therapy, and improve local anti-inflammatory effects. This paper investigates the efficacy of injection of sodium hyaluronate combined with compound betamethasone in knuckle articular cavity in KOA treatment, and analyzes its effect on patients' serum inflammatory factors, MMP-3, MMP-9 and prognosis of joint function.

The results showed that 34 patients in the observation group showed significant joint function recovery after combined treatment, and 21 patients showed significant improvement. The total effective rate of treatment was 91.67%, which was significantly higher than 80.00% of the control group. It proves that combination therapy can effectively relieve symptoms such as knee joint pain and accelerate healing (Wu *et al*., 2012). After treatment, the patients' VAS score and 20 m walking time were significantly reduced, and Lysholm score was increased significantly, which suggests that injection in knuckle articular cavity can take effect quickly. After combined

injection of compound betamethasone, the knee joint VAS and Lysholm scores were significantly better in the observation group. It may be due to the synergistic effect of compound betamethasone injection which inhibits the inflammatory response of joint injuries, reduces the exudation and accumulation of joint fluid, and prevents deterioration of local tissue lesions together with sodium hyaluronate. At the same time, the compound betamethasone as a lubricating fluid effectively avoids excessive damage caused by friction between the articular surfaces, thus promoting the repair and healing of articular cartilage (Hong *et al*., 2018; Shi *et al*., 2019).

Studies have confirmed that inflammatory factors IL-1β, IL-6, TNF-α and matrix metalloproteinases MMP-3 and MMP-9 play a role in the pathological progress of knee joint. After joint injury, local tissue inflammation is activated, and a large number of inflammatory mediators, such as IL-1β, IL-6, TNF-α, etc. are released by neutrophils, macrophages and monocytes (Zhao and Li, 2016; Zhao *et al*., 2005). In the progress of KOA, the above-mentioned inflammatory mediators have increased level in the serum, regulate and over activate the inflammatory-immune response, leading to further disease deterioration. At the same time, various matrix metalloproteinases MMP-1, MMP-3, and MMP-9 have increased expression in the articular cartilage and synovial membrane under the mediation of inflammatory factors, which in turn causes the degradation of articular cartilage matrix collagen fiber network and proteoglycan, aggravating damage and lesion of articular cartilage (Liu *et al*., 2018). This study found that after treatment, the patients' inflammatory factor level was significantly lower, and matrix metalloproteinases content was also significantly reduced ($P<0.05$). This suggests that injection in knuckle articular cavity inhibits the inflammatory process, while relieving degradation of articular cartilage matrix collagen fibers and protein. The observation group had superior improvement in IL-1β, IL-6, TNF-α, MMP-3, and MMP-9 levels than the control group, which further confirms that the combined treatment has better synergistic effect in anti-inflammatory and cartilage metabolism improvement than sodium hyaluronate alone (Zhang *et al*., 2018b). The follow-up results after treatment indicated that the adverse reaction rate was 3.33% (2/60) in the observation group, which was significantly lower than 15.00% of the control group.

## CONCLUSION

To conclude, significant therapeutic effect is observed in KOA patients treated with injection of sodium hyaluronate combined with compound betamethasone in knuckle articular cavity, which can effectively relieve pain and reduce serum inflammatory factors IL-1β, IL-6, TNF-α and matrix metalloproteinase MMP-3, MMP-9 contents, relieve knee arthritic excessive activation and protease degradation, reduce the incidence of adverse reactions, and promote the recovery of prognostic joint function.

*Statement of conflict of interest*

The authors have declared no conflict of interest.

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