

Clinical Study on the Effect of Dihuang Gutongkang Capsule on Oxidative Stress Factors in Knee Osteoarthritis

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Abstract: Eighty patients with knee osteoarthritis were randomly divided into a control group and an experimental group, with forty cases in each group, to observe the clinical effect of Dihuang Osteoarthritis Capsules on knee osteoarthritis (KOA). Both groups were treated with glucosamine hydrochloride capsules, and the experimental group was treated with Dihuang Osteoarthritis Capsule based on the treatment, and the treatment course was three months. Before and after the treatment, the clinical symptom scores and the changes of superoxide dismutase (SOD) and malondialdehyde (MDA) in the serum of each group were observed. Before treatment, there was no difference in the serum levels of SOD and MDA between the two groups. After treatment, the SOD of both groups was higher than before treatment, and the MDA was lower than before treatment. The difference was significant in the experimental group compared with the control group. The conclusion is that Di Huang Bone Pain Kang Capsules can effectively improve the serum SOD and MDA levels in patients with knee osteoarthritis, with an increase in the SOD level, a decrease in the MDA level, and a decrease in the VAS score and Lequesne index. Di Huang Bone Pain Kang capsule has a specific therapeutic effect on knee osteoarthritis, and its mechanism of action is related to the effect of serum oxidative stress factor.

Keywords: Dihuang Gutongkang capsule; Knee osteoarthritis; SOD; MDA

1. Introduction

Knee osteoarthritis (KOA) is a common clinical frequently occurring and chronic disease [1], which mostly occurs in middle and old age. The incidence of KOA in people over 60 years old and over 75 years old can be as high as 50% and 80%, respectively, with more female patients [2]. The lesion site is often in the synovium, articular cartilage, subchondral bone, etc. The lesion is mainly characterized by inflammatory destruction and hyperplasia of bone [3]. Clinical manifestations include joint stiffness, swelling, sitting up and down stairs, pain and discomfort, etc. In the late stage, patients may have permanent joint deformity, loss of normal life, and labor ability [4], causing a heavy economic burden to society and families. Western medicine generally uses non-steroidal anti-inflammatory drugs to treat KOA [5]. While these drugs may relieve pain quickly, long-term use may cause many digestive and other adverse reactions, and it is also easy to develop drug resistance and dependence. In recent years, the industry has gradually been concerned with traditional Chinese medicine in treating knee osteoarthritis with its significant clinical efficacy, less side effects, easy to take, low price, and other advantages, becoming the current hot direction of KOA treatment [6]. Traditional Chinese medicine believes that the fundamental pathogenesis of knee osteoarthritis is liver and kidney deficiency, blood stasis between the meridian muscle surface, tonic liver and kidney, blood circulation, and pain as the treatment principle [7]. Dihuang Gutongkang capsule is a hospital preparation summarized and developed by Zhao Yinglin, chief physician of the orthopedics and traumatology department of Xi'an hospital of Traditional Chinese Medicine. It has the effect of nourishing the liver and kidney, dredging collaterals, and relieving pain, and it has an obvious effect on patients with knee osteoarthritis [8]. Studies have shown that oxidative stress is related to the pathogenesis of KOA. Excessive oxidative stress produces a large amount of oxygen free radicals, causing chronic inflammation and leading to lesions of articular cartilage, subchondral bone, and synovium [9]. Currently, the clinical experimental research of Chinese patent

medicine in the treatment of KOA is mainly aimed at improving symptoms or signs of patients, and there are few studies on oxidative stress factors. Therefore, in this study, a controlled clinical experiment was designed to observe the differences in serum oxidative stress factor indexes SOD, MDA levels and knee joint VAS and Lequesne index scores between the two groups before and after treatment, and to evaluate the clinical efficacy of Dihuang Gutongkang Capsule in the treatment of KOA and its effect on serum oxidative stress factors. To explore the mechanism of Dihuang Gutongkang Capsule on KOA.

2. Clinical Data

2.1 General Data

Eighty patients with KOA who were treated in the outpatient and inpatient departments of Xi 'an Hospital of Traditional Chinese Medicine from September 2022 to April 2023 were selected. They were randomly divided into a control and experimental groups, with 40 cases in each group. There was no significant difference in general data (gender, age, course of disease) between the two groups ($P > 0.05$). See Table 1.

Table 1: Comparison of general data between two groups of KOA patients

Group	Cases No.	Gender (example)		Age(Years)			Disease courses(years)		
		Male	Female	Min	Max	Average($\bar{x}\pm s$)	Shortest	Longest	Average($\bar{x}\pm s$)
Control group	40	10	30	51	76	63.50±8.36	1	17	8.15±4.68
Experimental group	40	10	30	52	78	63.70±7.46	1	19	8.34±5.25

2.2 Diagnostic Standard

Refer to the diagnostic criteria for "knee osteoarthritis" in the Guidelines for the Diagnosis and Treatment of Osteoarthritis (2018 Edition) [10].

2.3 Inclusion Criteria

(1) Conform to the diagnostic criteria of knee osteoarthritis; (2) Age greater than 50 years old, both male and female ; (3) Knee joint without surgical treatment; (4) There were no other serious medical system diseases, and there was no allergy in the past use of these drugs; (5) Signed the informed consent ; (6) Can cooperate with the treatment, did not participate in other related clinical studies.

2.4 Excluded Criteria

(1) Allergic or hypersensitive to the drug composition; (2) Combined with nervous system diseases and severe liver and kidney dysfunction and other serious medical diseases; (3) Combined with rheumatic immune disease or traumatic arthritis and other joint lesions; (4) Had taken the same or similar drugs within two weeks before the start of the experiment; (5) Patients who did not meet the inclusion criteria and could not cooperate with the medication, sampling and efficacy follow-up of this experiment.

2.5 Suspension and Shedding Standards

(1) During the experiment, the treatment was not completed according to the regulations, and the data and other related case data were incomplete or missing; (2) During the experiment, the drug that may interfere with the experiment was taken by oneself, which affected the judgment of curative effect.

3. Research Method

3.1 Treatment Methods

Two groups of patients were given glucosamine hydrochloride capsules (Zhejiang Chengyi Pharmaceutical Co., Ltd., approved by H20143326) for oral treatment, 2 times a day, 1 capsule each time. On this basis, the experimental group was added with Dihuang Gutongkang Capsule [Xi 'an

Hospital of Traditional Chinese Medicine Hospital preparation, Shaanxi medicine control word (2001) No.1603], three times a day, four capsules each time, one month as a course of treatment, continuous treatment for three courses. During the observation period of treatment, the two groups were treated with basic treatment, including health education, knee function exercise, and hot compress, and other drugs that may affect the disease should not be used.

3.2 Efficacy Criteria

VAS Score and Lequesne Index Score were Assessed before and after Treatment.

(1) The visual analogue scale (VAS) score [11], the scoring criteria are as follows: 0 points do not feel any pain; there is a relatively mild pain sensation in 1-3 points, but this degree of pain can be tolerated; 4-6 points pain feeling although not too strong, bearable, will interfere with sleep; 7-10 pain feeling is very strong, seriously affecting the patient's diet and sleep.

(2) Lequesne index scoring standard[12], according to the international Lequesne scoring standard, the six aspects of joint rest pain (0-3 points), joint movement pain (0-3 points), tenderness (0-3 points), swelling (0-3 points), morning stiffness (0-3 points) and walking ability (0-6 points) were evaluated.

3.3 Observation Index

In the early morning 6: 30-7: 30 fasting state, extraction into the group of patients with elbow venous blood 2mL, placed in a clean tube. In the laboratory, the high-speed centrifuge was used for rapid centrifugation (3000 r / min , 10 min), and then the upper serum was separated and extracted by the drainage device. After labeling the groups and serial numbers, they were placed in the refrigerator at 80 °C for cryopreservation (try to avoid repeated thawing), and were extracted once before and after treatment. The content of SOD and MDA in synovial fluid was detected by enzyme-linked immunosorbent assay (ELISA). The instructions described the detection steps, and the kit was purchased from Shanghai Yuanju Biotechnology Center.

3.4 For Statistical Analysis

SPSS version 19.0 statistical software was used to statistically analyze the data. Measurement data were expressed as mean \pm standard deviation ($\bar{x}\pm s$). Data analysis was performed using the chi-square test and t-test. $P < 0.05$ can be considered as a statistically significant difference.

4. Result

4.1 Comparison of VAS Scores Between the Two Groups before and after Treatment.

Before treatment, the difference in VAS scores between the two groups was not statistically significant ($P > 0.05$). After treatment, the VAS scores of both groups were lower than before treatment, and the experimental group was lower than the control group. The difference between the groups was statistically significant ($P < 0.05$). See Table 2.

Table 2: Comparison of VAS scores between the two groups of KOA patients before and after treatment ($\bar{x}\pm s$, points)

Group	Cases No.	Period	Vas score
Control group	40	Before treatment	2.08 \pm 0.76
		After treatment	1.23 \pm 0.80 [#]
Experimental group	40	Before treatment	2.10 \pm 0.77
		After treatment	0.88 \pm 0.68 ^{#*}

Note: Compared with the group before treatment, [#] $P < 0.05$; Compared with the control group, ^{*} $P < 0.05$

4.2 Comparison of Lequesne Index Scores between the two Groups before and after Treatment

Before treatment, the two groups had no significant difference in Lequesne score ($P > 0.05$). After treatment, the Lequesne scores of the two groups were lower than those before treatment, and the experimental group was lower than the control group. The difference between the groups was statistically significant ($P < 0.05$). See Table 3.

Table 3: Comparison of Lequesne index scores between the two groups of KOA patients before and after treatment ($\bar{x}\pm s$, points)

Group	Period	Rest pain	Motor pain	Pressing pain	Selling	Morning stiffness	Walking ability	Total score
Control group	Before treatment	1.62±0.48	1.78±0.56	1.53±0.51	1.49±0.43	1.45±0.57	2.57±0.92	8.47±2.25
	After treatment	1.43±0.29 [#]	1.56±0.45 [#]	1.18±0.50 [#]	1.15±0.38 [#]	1.31±0.38 [#]	1.87±0.58 [#]	6.65±1.86 [#]
Experimental group	Before treatment	1.58±0.44	1.72±0.52	1.58±0.55	1.45±0.40	1.41±0.53	2.63±0.95	8.52±2.32
	After treatment	0.95±0.19 ^{#*}	0.98±0.42 ^{#*}	0.82±0.48 ^{#*}	0.76±0.21 ^{#*}	0.97±0.24 ^{#*}	1.35±0.49 ^{#*}	5.83±1.33 ^{#*}

Note: Compared with the group before treatment, [#]P<0.05; compared with the control group, ^{*}P<0.05

4.3 Comparison of MDA and SOD Levels between the two Groups before and after Treatment.

Before treatment, there was no significant difference in MDA and SOD levels between the two groups ($P > 0.05$), and there was no statistical significance. After treatment, the content of MDA decreased and the content of SOD increased in both groups. The comparison between the groups showed that the MDA level in the experimental group was lower than that in the control group, the level of SOD was higher than that of the control group, and there was significant difference, and there was statistical significance ($P < 0.05$). See Table 4.

Table 4: Comparison of serum SOD and MDA levels before and after treatment in two groups of KOA patients ($\bar{x}\pm s$)

Group	Cases No.	Period	SOD(U·mL ⁻¹)	MDA(nmol·mL ⁻¹)
Control group	40	Before treatment	110.02±10.26	6.92±0.67
		After treatment	115.38±10.42 [#]	6.59±0.59 [#]
Experimental group	40	Before treatment	108.36±10.77	6.77±0.68
		After treatment	120.88±12.23 ^{#*}	6.30±0.49 ^{#*}

Note: Compared with the group before treatment, [#]P<0.05 ; compared with the control group, ^{*}P<0.05

5. Discussion

The diagnosis of KOA and the role of related serum factors in the pathogenesis of the disease have been the direction and focus of clinical research in recent years. The traditional diagnosis depends on the patient's symptoms, signs, and X-ray examination. It is of great clinical significance for the diagnosis, treatment, and efficacy evaluation of KOA to study the role of related serum factors in the pathogenesis of KOA. It has been found that the accumulation of oxygen free radicals caused by excessive oxidative stress is one of the important factors of articular cartilage degeneration in the development of knee osteoarthritis [13]. Oxygen free radicals easily react with intracellular proteins, lipids, and other biological macromolecules, causing oxidative damage, thereby inhibiting the formation of chondrocytes and accelerating degradation, reducing the synthesis of cartilage proteoglycans and matrix collagen, and ultimately leading to knee cartilage damage degeneration [14]. In addition, oxygen free radicals can also inhibit the proliferation of chondrocytes and aggravate the symptoms of knee osteoarthritis [15]. The levels of active factors such as MDA and SOD in the body are important indicators of oxidative stress evaluation. The abnormal degree of lipid oxidation will increase the level of MDA, so the MDA value reflects the degree of damage to the human body caused by oxygen free radicals. On the contrary, SOD can decompose and consume oxygen free radicals, neutralize the oxidative damage caused by free radicals, repair cells, and eliminate lipid peroxidation [16-17]. The level of MDA in the serum of KOA patients is significantly higher, while the activity of SOD is significantly lower than that of healthy people, indicating that the oxidative stress reaction with SOD and MDA as the main participants is highly correlated with the development of KOA [18-19].

Glucosamine is the basic substance for the synthesis of glycosaminoglycans (GAG). Glycosaminoglycans, including chondroitin sulfate and hyaluronic acid, are the key components for the formation of proteoglycans in articular cartilage. Therefore, timely supplementation of glucosamine after the onset of KOA can promote the metabolism of chondrocytes and accelerate the synthesis of related proteins, thereby delaying cartilage degradation, improving joint structure, and protecting cartilage tissue [20]. Although glucosamine has a certain effect on the treatment of knee osteoarthritis, as a nutrient component, it needs the absorption and utilization process of the human body, so the effect is relatively slow, and it is difficult to improve the symptoms of joint swelling and stiffness [21]. Traditional Chinese medicine is treated from the pathogenesis of KOA. Combining traditional Chinese and Western medicine

can better and faster improve clinical symptoms and joint motor function better and faster [22]. Rehmanniae Gutongkang Capsule is derived from the Zuogui Pill of "Jingyue Quanshu", which nourishes kidney yin and replenishes essence to fill marrow. Antler glue tonic essence blood, warm kidney;

Duzhong and Chuanniuxi tonify the liver and kidney, strong bones, while Chuanniuxi can activate blood circulation and lead medicine into the meridian; Angelica blood activates blood; white peony root nourishes blood and astringes yin, softens the liver, and relieves pain; Ramulus Cinnamomi warms the meridians, helps Yang, and dispels cold. A variety of traditional Chinese medicines collocate together to benefit the liver and kidney, dredging collaterals and relieving pain, strong bones, and strong bones. Modern medical research shows that the glycosides contained in Radix Rehmanniae Preparata have anti-inflammatory and protective effects on cartilage [23]. The antler polypeptides in antler glue can increase the activity of SOD and reduce the concentration of MDA [24-26]; The riboflavin in Medicinal Cyathula Root can increase the vitality of antioxidant enzymes [27], and the rich Angelica sinensis ketone and ferulic acid in Angelica sinensis can eliminate free radicals [28]; Paeoniflorin, a pharmacological component of Paeoniae Radix Alba, has significant anti-inflammatory and immunomodulatory functions [29-30].

6. Conclusion

In summary, Dihuang Gutongkang capsule combined with glucosamine capsule in treating KOA can significantly improve patient's clinical symptoms and reduce VAS and Lequesne index scores. The control experiment showed that the mechanism of Dihuang Gutongkang Capsule on KOA was related to the reduction of serum MDA level and the increase of serum SOD level, and it had a regulatory effect on serum oxidative stress response in KOA patients. The curative effect of Rehmanniae Gutongkang Capsule in treating KOA is reliable, and it has the value of further research and promotion.

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