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Original Article

Effects of continuous passive motion on Mankin's score and histopathology of knee osteoarthritis in rabbits

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Abstract: Objective: To explore the effects of continuous passive motion (CPM) on the Mankin's score and histopathology of knee osteoarthritis (OA) in rabbits. Methods: 20 model rabbits with OA were randomly divided into OA model group (n = 10) and OA+CPM group (n = 10). Rabbits in OA group received normal feeding, while rabbits in OA+CPM group received knee joint passive motion on CPM training instrument. After intervention, the histopathological changes of chondrocytes were observed, and Mankin's score was evaluated. Electronic microscope was used to observe the ultrastructural changes of cartilage, so as to compare the range of flexion motion (RFM) of rabbits' knee joint before and after intervention. Reverse transcription-polymerase chain reaction (RT-PCR), western blot and immunohistochemistry were used to detect the level changes of malondialdehyde (MDA), superoxide dismutase (SOD), interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), matrix metalloproteinase 1 (MMP-1) and collagen 2 (Col-2) before and after intervention (These methods were not described in the Materials and Method section and the expression levels of designated genes in Figure 6 and 7 were not detected by RT-PCR), western or IHC). Results: After intervention, the range of flexion motion of knee joint in OA+CPM group was higher than that in OA group ($P < 0.05$), and the gross morphology and micromorphology of cartilage in OA+CPM group were better than those in OA group. The Mankin's score, MDA, IL-1β, TNF-α and MMP-1 of cartilage in OA+CPM group were lower than those in OA group ($P < 0.05$), and the SOD and Col-2 of cartilage were higher than those in OA group ($P < 0.05$). Conclusion: Continuous passive motion can effectively improve the symptoms of knee osteoarthritis and enhance the range of motion of rabbits' knee joint. The mechanism may be related to the fact that continuous passive motion can relieve the excessive secretion of peroxide and inflammatory state in the lesion site.

Keywords: Continuous passive motion, osteoarthritis in rabbit knee joint, Mankin's score, histopathology, influence

Introduction

Osteoarthritis (OA) is a chronic, progressive, and degenerative joint disease characterized by degeneration of articular cartilage and synovitis, causing joint pain and dysfunction. In severe cases, total joint replacement should be performed. Clinical practice has found that OA is the most common joint disease of the elderly. Among people over 50 years old, OA is second only to cardiovascular disease that causes long-term disability, which seriously affects the health status and quality of life of patients, imposing great social and economic burdens on society and individuals [1-3].

Many clinical treatment options are available for OA. Oral medications can relieve patients' symptoms in a short period of time, but most of which relieve pain and inflammation and have no obvious effect in improving and repairing the degradation of articular cartilage; a hyaluronic acid-based product could be injected into an arthritic joint to improve the pain, swelling and stiffness associated with arthritis. However, there is no strong evidence that it can delay the development of OA and promote the regeneration of articular cartilage [4, 5]. Surgical treatment can fundamentally cure OA, but the cost, risks and complications of surgery could not be neglected. It is only suitable for patients with advanced OA and severe symptoms. Therefore, it is urgent to seek low-cost non-drug therapies with low side effects and drug therapy to promote articular cartilage

repair and delay the progress of OA through comprehensive strategies [6, 7].

CPM is one of the emerging OA interventions in recent years. Clinical practice has found that excessive high-intensity exercise can cause or accelerate the occurrence of OA while scientific and reasonable exercises have a positive effect on the treatment of OA. A systematic review of the effect of exercise on knee OA revealed that exercise can significantly relieve knee pain in patients. A meta-analysis with a comparison of 5627 cases of analgesic drug treatment and 4179 cases of exercise therapy showed that the two options exhibited similar efficacy in relieving joint pain [8, 9]. Studies has confirmed that CPM can prevent joint adhesion, accelerate the regeneration and repair of intra-articular cartilage, and is conducive to postoperative rehabilitation on limb function and the improvement of quality of life. It is believed that CPM can be used in OA patients with limited mobility and rehabilitation treatment. It presents better efficacy than traditional long-term fixed therapy and can be performed when OA patients' anesthesia has not resolved [10, 11]. Although there are many studies about the role of CPM in OA and the mechanism remains unclear, which has affected its clinical application. This study aims to analyze the effect of CPM on osteoarthritis in rabbit knee joint and analyze its mechanism, in order to provide a theoretical reference for promoting the clinical application of CPM therapy.

Material and methods

Animal scouring

New Zealand white rabbits aged 3 to 4 month old, weighing 1.9 to 3.2 kg, were purchased from Shanghai Jiagan Biological Technology Co., Ltd., and fed with adequate food and water in separate cages at constant 25°C, humidity 50%. The experimental procedures were approved by the animal research department of Cangzhou People's Hospital.

Experimental method

Animal model preparation: Intravenous injection was performed on marginal ear vein with 50 g/L ketamine at a dose of 100 mg/kg. A transverse incision was made on the medial knee joint into the joint cavity in the experimental group. The medial collateral ligament, anterior and posterior cruciate ligament and the medial meniscus were cut off and sutured. Penicillin was given for three consecutive days to prevent infection.

Grouping: After successful modeling, 20 white included rabbits were divided into the OA and the OA+CPM groups according to the random number table method. Each group had 10 large white rabbits. OA group weighted 2.01-3.11 kg, with an average body mass (2.31 ± 0.18) kg, while OA+CPM group weighted 1.9-3.2 kg, with an average body mass of (2.29 ± 0.19) kg. There was no significant difference in body mass between the two groups of rabbits ($P>0.05$).

Experimental intervention

The white rabbits in the OA group were only fed normally. The white rabbits in the OA+CPM group received 4 hours of CPM each morning and evening for 4 weeks.

Observation indicators

RFM before and after intervention: The neutral-zero method was used to calculate the knee flexion angle of the two groups as follows. Using double-arm protractor, the axle center of the protractor was aligned with the center point of the joint, and the two arms were aligned with axes of the limb. The keen joint is taken as the neutral position while 0° represents the straight position. The distance the movable joint moves away from the 0° position was recorded as the RFM.

Observation of keen joint morphology: At the end of the treatment, they were killed by the air embolism method. Joint was opened up along the anterior midline of the knee joint to observe the general condition of the articular cartilage-related indicators, including the amount of effusion, the cartilage surface and synovium. Then, the distal femur was fixed with 10% formaldehyde and colored by HE staining, The morphology of the knee cartilage was observed under the electron microscope.

Mankin score of knee joint cartilage before and after intervention: The status of knee articular cartilage of the two groups of white rabbits were evaluated with Mankin's score

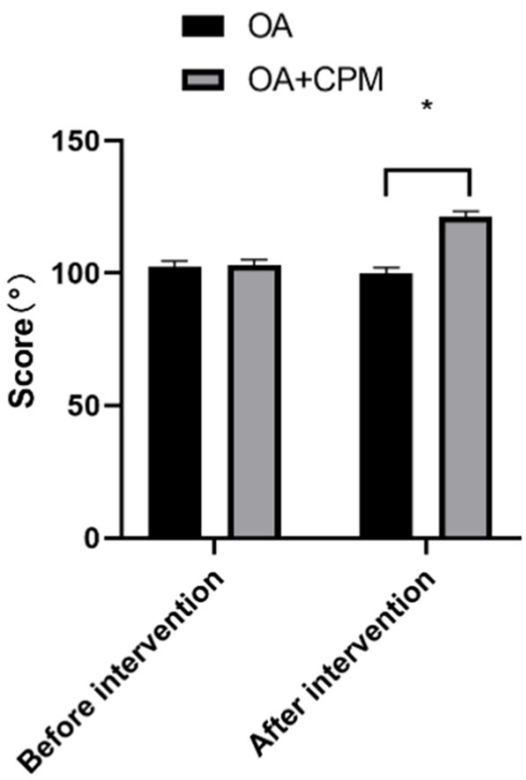

Figure 1. Analysis of RFM before and after intervention in the two groups of white rabbits. *P < 0.05.

before and after intervention with the following criteria: 0 point represent normal cartilage tissue, smooth surface, uniform distribution of chondrocytes, without loss of stains; 2-7 points represent mild damaged cartilage, small fissures in the surface, hypertrophic chondrocytes in the middle and deep layers, and loss of stains; 8-12 points represent moderate damage, uneven surface, open wide fissures in middle and deep layers, clustered chondrocytes, uneven and loss of stains in the surface and middle and deep layers; 13-14 points represent severe damage, thinner surface layer, deep fissures in the subchondral bone, disordered cell arrangement, a large number of clustered chondrocytes, uneven, and obviously out of stains [12].

Changes in indicators before and after intervention: Blood samples of two groups were collected before intervention and after 4 weeks of intervention. RT-PCR, western blot and immunohistochemical (There are no descriptions for these methods and the expression level of these genes were not showing) methods were used to analyze the expression of OA-related oxidative stress, inflammatory factors and collagen metabolic factors, including MDA, SOD, IL-1β, TNF-α, MMP-1 and Col-2.

Statistical method

SPSS Statistics (IBM Corporation, Armonk, USA) was used for statistical analysis. Measurement data ($\bar{x} \pm s$) were compared by Student's t test, and Counting data [n (%)] were examined by chi-square test. $P < 0.05$ denotes significant difference [13].

Results

Analysis of RFM before and after intervention

RFM did not differ between two groups before intervention (P>0.05). After 4 weeks of intervention, RFM of the white rabbits in the OA+CPM group was higher than that before intervention (P < 0.05). RFM did not change significantly in the OA group, and decreased a little (P>0.05). After 4 weeks of intervention, OA+CPM group showed greater RFM than that of OA group (P < 0.05) (**Figure 1**).

General morphological changes of knee joint cartilage after intervention

At the fourth week of intervention, the knee joint capsule was opened in two groups. The articular surface of the knee cartilage of the OA group white rabbits was rough, the cartilage appeared scattered erosion in gray color with obvious joint effusion and swollen synovial membrane was swollen; The articular surface of the white rabbits in the OA+CPM group was rough but better than that in the OA group. It was slightly rougher and brighter, with a small amount of fluid in the joint cavity (**Figure 2**).

Changes of knee joint cartilage micromorphology after intervention

At the 4th week of intervention, the chondrocytes in the OA group were extremely unevenly distributed, the surface layer became thin and uneven, and the cartilage tide line was interrupted. There are fissures deep into the middle of the joint surface, and clusters of chondrocytes can be seen; while the surface layer of the knee joint cartilage of OA+CPM group is thicker than that in the OA group, the chondro-

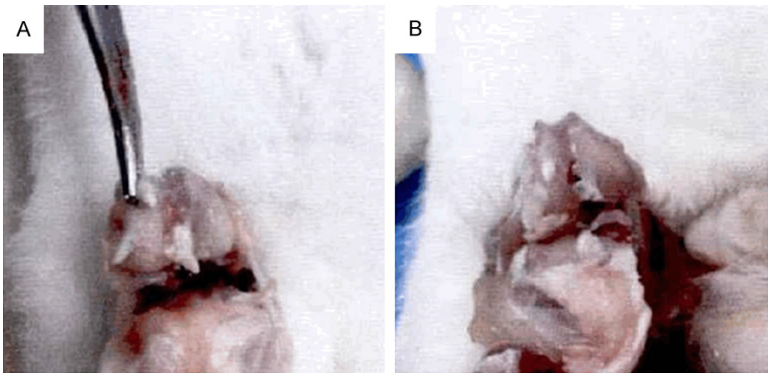

Figure 2. The general morphological changes of the articular cartilage of the two groups after intervention. A. OA group. B. OA+CPM group.

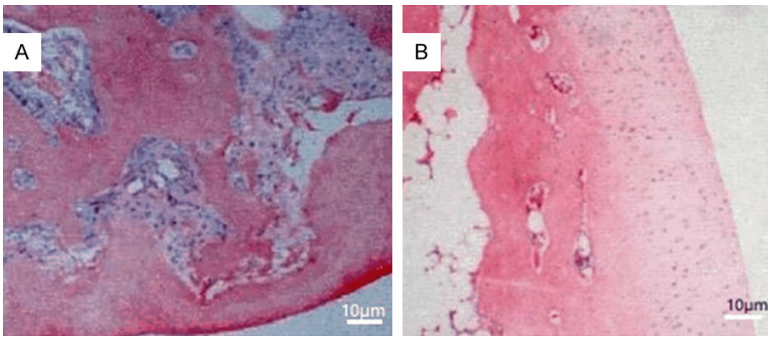

Figure 3. The changes of knee joint cartilage micromorphology after intervention of two groups. A. OA group. B. OA+CPM group.

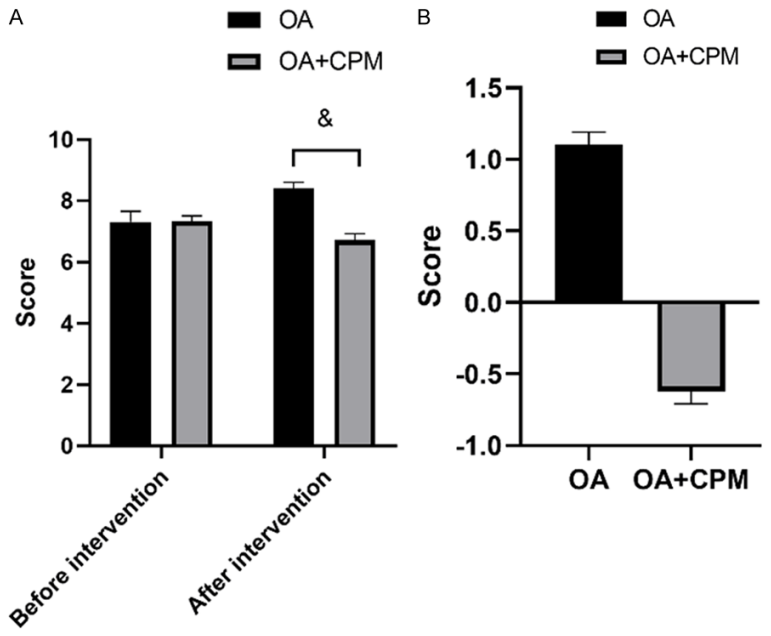

Figure 4. Comparison of Mankin's score changes between the two groups before and after intervention. After 4 weeks of intervention, the Mankin's score of OA+CPM group was lower than that of the OA group ($P < 0.05$) (A); the Mankin's score of OA group showed a positive increase, and OA+CPM group showed a negative increase (B); &$P < 0.05$.

cytes are arranged relatively uniformly, and the tide line is intermittent (**Figure 3**).

Changes of Mankin's score before and after intervention in two groups

It was found that the Mankin's scores of the two groups before the intervention were not significantly different ($P>0.05$). After 4 weeks of intervention, Mankin's scores of OA group were significantly higher than those before the intervention. ($P < 0.05$), and the Mankin's scores of OA+CPM group were significantly lower than before intervention, ($P < 0.05$); Meanwhile, OA+CPM exhibited lower Mankin's score than OA group ($P < 0.05$) (**Figure 4**).

Changes of oxidative stress indexes before and after intervention

After blood sample collection and laboratory analysis, it was found that the MDA and SOD levels before the intervention were not significantly different between two groups ($P>0.05$). After 4 weeks of intervention, MDA levels showed a decrease trend while SOD levels showed an increase trend in OA+CPM and OA groups ($P < 0.05$). We found that the MDA level of OA+CPM group after 4 weeks of intervention was lower, and the SOD level was higher than that of OA group ($P < 0.05$) (**Figure 5**).

Analysis on the changes of inflammatory factors before and after intervention

The levels of IL-1β and TNF-α in the blood samples of the two groups of white rabbits

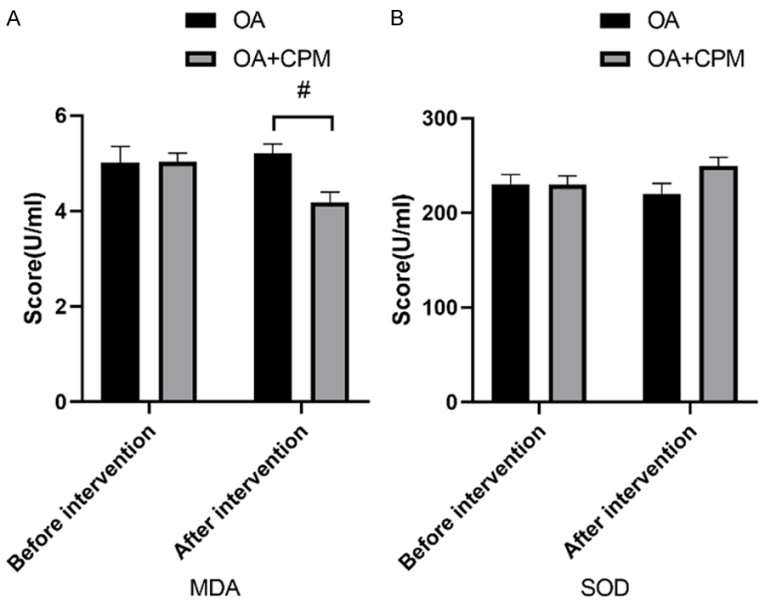

Figure 5. Analysis of the changes in oxidative stress indicators before and after intervention. MDA level decreased in the OA+CPM group and increased in OA group (A); SOD level of the OA+CPM group increased, and the SOD level of the OA group after intervention decrease after intervention (B); #P < 0.05.

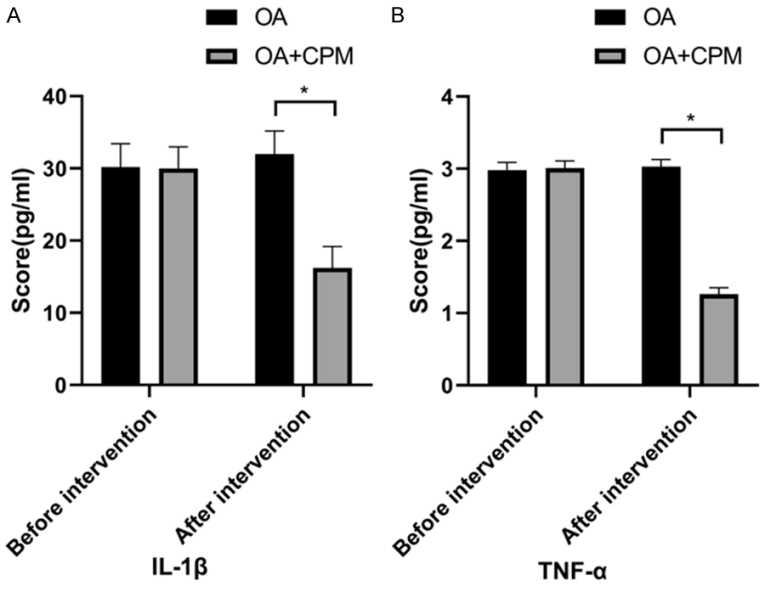

Figure 6. Analysis of changes in inflammatory factor indexes before and after intervention. The levels of IL-1β and TNF-α in OA+CPM group were significantly lower than those before treatment (P < 0.05), while they were slightly higher than those before treatment in OA group (P>0.05). The IL-1β and TNF-α levels of OA+CPM group are lower than those of OA group after 4 weeks of intervention (A, B); *P < 0.05.

before intervention were not significantly different (P>0.05). After 4 weeks of intervention, we found that the levels of IL-1β and TNF-α in the OA+CPM group were significantly lower than those before treatment (P < 0.05), and were slightly higher in the OA group (P>0.05). The IL-1β and TNF-α levels of the OA+CPM group were significantly lower than those in the OA group (P < 0.05) (**Figure 6**).

Analysis of the changes of the glial metabolism indexes of the two groups before and after intervention

We found that the levels of MMP-1 and Col-2 in the blood samples of the two groups before the intervention were not significantly different (P> 0.05). After 4 weeks of intervention, MMP-1 levels of OA+CPM group were significantly lower than those before treatment, and the Col-2 levels were significantly higher than those before treatment (P < 0.05). However, the MMP-1 and Col-2 levels of OA group were slightly higher than those before treatment. In general, the two indicators did not change significantly compared with those before treatment (P>0.05) (**Figure 7**).

Discussion

Osteoarthritis (OA) is also known as degenerative osteoarthropathy, degenerative arthritis, senile arthritis, hypertrophic arthritis, etc. It could be induced by advanced age, fat, injury, congenital abnormalities of joints, and joint deformities. It tend to occur in middle-aged and elderly people, and the most affected joints are those bear the heavy weight and move frequently (such as knee joint, hip joint, etc.), its typical clinical manifestations are pain, stiffness in joints. Patients often experience pain

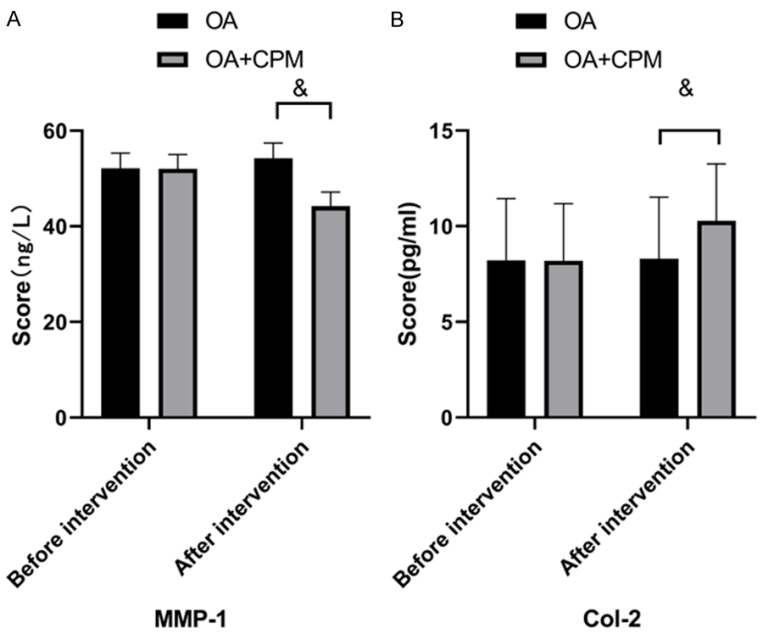

Figure 7. Analysis of changes in glial metabolism indexes of the two groups before and after intervention. The levels of MMP-1 and Col-2 in the two groups before intervention were not significantly different (P>0.05). After 4 weeks of intervention, it was found that MMP-1 level of OA+CPM group was significantly lower than that before treatment, and the MMP-1 level of OA group was partially increased compared with before intervention. (P < 0.05) (A); the level of Col-2 differs significantly between two groups after intervention (P < 0.05) (B); &P < 0.05.

after rest and feel relieved after some activities. But excessive activity will cause more severe pain [14-16]. With the deepening of social aging in China, the incidence of OA has also shown a gradual increasing trend. The data shows that the incidence of knee OA in people aged 60-75 in China is as high as 50%, and in people over 75 years old, it could even increase to 75%. OA will obviously affect the normal movements, leading to a sharp decline in their quality of life, and also bring a greater burden to society [17, 18].

The pathogenesis of OA is still unclear, but most studies believe that genetic and environmental factors, age, obesity, etc. have played an important role in the occurrence of OA. There is no sovereign remedy for OA, and relieving pain and delaying the progress of the disease are the main effects of current treatment options [19]. For example, Western medicine advocates taking non-steroidal anti-inflammatory drugs and glucosamine hydrochloride capsules, if necessary, it can be treated with hyaluronic acid injection in the joint cavity. For those with more serious condition, it is recommended to receive surgical treatment such as high tibia osteotomy or intra-articular debridement. However, the effects are not satisfactory.

In recent years, the pathogenesis of OA has been studied in detail with molecular biology, genetics and immunology, and a variety of new interventions have also been gradually applied for OA. Exercise therapy refers to the use of equipment, freehand, or the patient's own strength to perform certain exercise (active or passive exercise, etc.) to enable the recovery of motor function and sensory function recovery. Exercise therapy is used as an intervention to carry out a variety of trainings for patients. It has become one of the core means of rehabilitation treatment [20, 21]. In fact, it was believed that patients with OA need to receive long-term fixed treatment, but this often leads to muscle atrophy, joint spasm, and intra-articular adhesions which hinder the recovery of the joint function, and even increase the risk of joint stiffness. Passive motion is therapeutic exercise technique used to move a patient's joint through a range of motion without the patient's use of the involved extremity. The motion is accomplished by a therapist, an assistant, the use of a machine, or by the patient's use of the non-involved extremity. The orthopedic expert Salter's data points out that passive motor is conducive to accelerating the recovery of postoperative limb function and the improvement of quality of life in patients with OA. Studies also pointed out that regular passive motion can help relieve joint pain and stiffness in patients with OA, and improve the joint mobility of patients, and the treatment effect is better than traditional long-term fixed therapy [22, 23].

This study explored the effect of CPM on the Mankin's score and histopathology of arthritis

by establishing OA models of white rabbits. The results showed that compared with the OA group, the white rabbits in the OA+CPM group were significantly superior in terms of joint effusion, synovial swelling, and cartilage color, suggesting that CPM accelerated repair progress of articular cartilage and improved the inflammatory state. Some studies have revealed that CPM could promote the metabolism of chondrocytes, accelerate the synthesis of cartilage matrlx protein, thereby helping the reconstruction of damaged cartilage, reducing intra-articular adhesions, and promoting the elimination of lysosomal enzymes and inflammatory exudates. These are similar to the results of this study [24]. We also found that after intervention, the RFM of the OA+CPM group was significantly higher and the Mankin's scores were significantly lower than those in the OA group, which is also linked to the fact that CPM could improve the inflammation status of rabbit knee, which accelerates the reconstruction of cartilage tissue.

This study also explores the mechanism by which CPM intervention can improve the symptoms of knee arthritis in OA models of rabbits. We found the MDA level of decreased and the SOD level increased in OA group after intervention. Studies have found that the free radicals (oxidative stress) play an important role in the pathological process of OA. Excessive free radicals will cause oxidative or nitrifying injury, leading to overexpression of MDA, protein hydroxyl levels, resulting in depolymerization of hyaluronic acid, decreased viscosity of joint synovial fluid, inactivation of anti-protease, induction of bone resorption and even cartilage degradation, and eventually form OA. This study suggests that CPM helps reduce MDA Level and increase SOD level, suggesting that CPM can effectively improve the actual secretion of oxygen free radicals in OA models of rabbits [25]. We also found that the inflammatory status of OA rabbits, such as IL-1β and TNF-α levels after CPM intervention has been improved very well, which also echoes the results of other studies. Finally, the comparison of the glial metabolism indexes between the two groups suggested that CPM can also accelerate the repair of damaged cartilage by regulating glial metabolism. Some studies have found that resistance exercise (strength training) could reduce the inflammatory markers, high-sensitivity C-reactive protein and MMP-13 levels, and inhibit the degradation of articular cartilage regulated by TNF-α, thereby reducing the knee injury index and improving the clinical symptoms of OA. The results are similar to our study. The dynamic balance between MMPs and tissue inhibitors of metalloproteinases in cartilage plays an important role in maintaining the structural integrity of cartilage. MMP-1 is generally expressed on the surface of cartilage and is also an important indicator of cartilage matrix metabolism [26]. Studies have indicated that the serum MMP-1 level of OA model will continue to be highly expressed with the prolongation of the modeling time. Therefore, the results in this study suggest that CPM helps to accelerate cartilage repair and joint function recovery in OA.

In summary, CPM can effectively improve the symptoms of arthritis in rabbit knee joints and increase the joint mobility. The underlying mechanism may be related to the fact that CPM improves the excessive secretion of peroxide and inflammation status in the lesion. The shortcomings of this study are as follows: (1) The small sample size results in a lack of comprehensiveness; (2) No long-term follow-up was performed. The next step is to carry out animal experiments with a larger sample size and longer observation time.

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Disclosure of conflict of interest

None.

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