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Original Article

The repair effect and mechanism of continuous passive motion on osteoarthritis in a rabbit model

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Abstract: Objective: To observe the effect of continuous passive motion (CPM) on osteoarthritis in a rabbit model and explore its mechanism. Methods: Thirty healthy rabbits with a total of 60 knee joints were randomized into three groups. Group A had CPM for 8 h daily, starting on postoperative day 1 and free movement in the cage, group B received CPM for 2 h daily, starting on postoperative day 1 and free movement in the cage, and group C only had free movement in the cage. Mankin's score was used to compare the gross morphology of the rabbit's knee joint. Malondialdehyde (MDA) and superoxide dismutase (SOD) were measured by RT-PCR and western blot method before and after intervention. Results: The Mankin's scores of rabbits in groups A and B were significantly lower than those in group C, and those in group A were lower than those in group B at week 4 and week 12 of intervention ($P<0.05$). At week 4 of the CPM intervention, the gross morphological scores were the highest in group A, followed by group B, and the lowest in group C ($P<0.05$). At week 12 of CPM intervention, the gross morphological scores of the knee joints in groups A and B were increased again, which were the highest in group A, followed by group B, and the lowest in group C ($P<0.05$). At week 12 of intervention, MDA levels in group A were lower than those in groups B and C, whereas SOD levels in group A were higher than those in groups B and C. Conclusion: CPM can effectively improve the symptoms of knee osteoarthritis in rabbits and increase the mobility of the joints, and the mechanism may be related to the ability of CPM to reduce the overproduction of peroxide at the lesion site.

Keywords: Continuous passive motion, osteoarthritis malondialdehyde, superoxide dismutase

Introduction

Knee osteoarthritis (KOA) is a chronic, progressive and degenerative knee joint disease [1], which is characterized by degenerative changes of articular cartilage and synovial inflammation. Most patients suffer from joint pain and dysfunction, and total joint replacement may be required when the condition is severe. In practice, KOA is the most common joint disease in the elderly, and among people aged over 50 years old. KOA is second only to cardiovascular disease leading to long-term disability, seriously affecting the health and quality of life of patients and increasing social and economic burden, and data show that by 2020, KOA may become the fourth most disabling disease in China [2, 3].

Currently, there are many treatments for KOA. Oral medications have short-term relief effects for patients, but most of the clinical medications for KOA can only relieve pain and inflammatory symptoms, and have no significant effect in reducing articular cartilage degeneration and repairing damaged articular cartilage [4]. Injecting Hyaluronic acid into the joint cavity can relieve pain by lubricating the joint and reducing friction, but there is no strong evidence that it delays disease progression and promotes articular cartilage regeneration [5]. Physical interventions such as acupuncture and massage are more effective in improving joint mobility and reducing joint pain, but are mainly used in patients with mild symptoms [6]. Surgical treatment can fundamentally cure KOA, but it is costly and risky, and is only applicable to advanced KOA patients with severe symptoms. Therefore, the search for non-pharmacological therapies with low side effects and cost-effectiveness, as well as the development of a comprehensive treatment strategy to effec-

tively treat or delay the progression of KOA has become an urgent issue [7].

Continuous passive motion (CPM) is one of the emerging interventions for KOA. It has been found in clinical practice that although excessive high-intensity exercise can cause or accelerate the occurrence of KOA, scientific and reasonable exercise and sports have positive effects on symptoms of KOA [8]. A systematic review of the effects of exercise on KOA showed that exercise significantly reduced knee pain in patients, and a meta-analysis of KOA compared 5627 patients treated with pain medication and 4179 patients treated with exercise therapy showed that the two treatments were similar in relieving joint pain [9]. Studies have confirmed that CPM can prevent joint adhesions, accelerate the regeneration and repair of intra-articular cartilage, and facilitate the recovery of postoperative limb function as well as the improvement of quality of life. It is believed that CPM can be used for KOA patients with limited mobility and postoperative rehabilitation of KOA, and its efficacy is superior to traditional long-term immobilization therapy, which can be performed when postoperative anesthesia has not yet subsided in KOA patients [10, 11]. Although there are some studies on the application of CPM in KOA, its mechanism is still unclear, which affects its clinical promotion to a certain extent. The aim of this study was to analyze the effect of CPM on KOA in rabbits and explore its mechanism, in order to provide theoretical reference for accelerating the promotion of CPM therapy.

Materials and methods

Experimental animals

Thirty 3-month-old purebred New Zealand rabbits were purchased from Bignon Animal Breeding Co., Ltd. The average body weight of the experimental rabbits was (2.01±0.43) kg, and each rabbit was kept in a separate cage and fed freely. Thirty rabbits were then divided into groups A, B and C, with 10 rabbits in each group for a total of 20 knee joints. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This study was approved by the Committee on the Ethics of Animal Experiments of Cangzhou People's Hospital (No. NCT01586327).

Establishment of model of total cartilage defect in the knee joint

The rabbits were fixed in supine position on the operating table and anesthetized by 3% pentobarbital sodium (1 mg/kg) via ear vein, and the hair at both knee joints was shaved under aseptic conditions. After disinfection, an arc-shaped incision was made on the medial aspect of the patella of the rabbit's knee, layer by layer, to the joint capsule. After the patellar surface of the femur was exposed, a total cartilage defect with a diameter of about 3 mm was made using an orthopedic surgical electric rotation, centered on the medial condyle. The wound was rinsed clean with physiological saline and then sutured layer by layer, and postoperative gentamicin was used to prevent infection (200,000 U daily, 1 time/d for 7 d).

Experimental intervention

Thirty rabbits were then randomized into groups A, B and C (10 rabbits and 20 knees in each group). Rabbits in group A were subjected to 8 h of daily CPM (one session lasted 2 min at a frequency of 60 beats/min every 20 min, with 4 h in the morning and 4 h in the afternoon) starting from the 1st postoperative day, and moved freely in the cage during the rest of the time. Rabbits in group B received 2 h of CPM daily on postoperative day 1 (the frequency was the same as group A, with 1 h in the morning and 1 h in the afternoon) and moved freely during the rest of the time in cage. Rabbits in group C could move freely in the cage without CPM.

Specimen handling and observation indicators

At week 4 and week 12 of CPM intervention, 5 rabbits (10 knees) were sacrificed respectively with air embolization under anesthesia. The experimental rabbits were anesthetized with 30% urethane (3-4 mL/kg), and then sacrificed by air injection through ear margin vein. The following indicators were observed.

Body weight

Body weight before intervention, at week 4 and week 12 of CPM intervention was assessed by Mettler AE100 Analytical Balance (Mettler Toledo, Columbus, OH, USA).

Mankin's score

Mankin's score before intervention, at week 4 and week 12 of CPM intervention was evaluat-

Table 1. Comparison of baseline data ($\bar{x}\pm s$)/[n (%)]

Baseline data		Group A (n=20)	Group B (n=20)	Group C (n=20)	F/X^2	P
Gender	Female	10	9	8	0.404	0.817
	Male	10	11	12		
Mean body mass (kg)		2.00±0.12	2.01±0.13	2.03±0.12	0.306	0.737
Articular flexion (°)		140.11±7.69	139.28±7.89	141.11±7.59	0.281	0.756

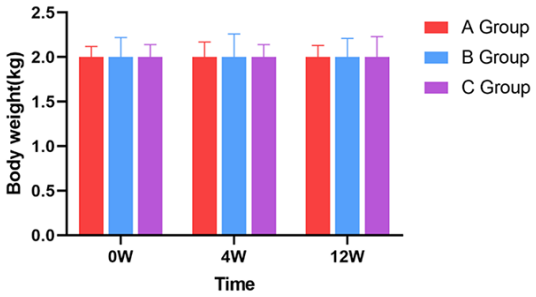

Figure 1. Body weight of the rabbits in three groups. The differences among three groups before surgery, at the 4th week and at 12th week of CPM intervention were not statistically significant (P>0.05). n=5 rabbits (10 knees) each group.

ed, respectively [12]. The specific evaluation method was as follows: tissues of about 4×4×3 mm^3 in size were taken from the defect area and its surroundings, and the specimens were immersed in 10% neutral formalin solution and fixed for 24 h. After full immersion with 10% phosphate buffer saline (PBS) buffer, the specimens were decalcified with ethylene diamine tetraacetic acid (EDTA) for 4 weeks, and then rinsed with tap water to remove the residual EDTA and soaked overnight in 0.2 mmol/L phosphate buffer. The specimens were fixed and embedded in paraffin, and then sectioned continuously in 4-10 μm thickness using RM2015 microtome (Leica, Germany). Afterwards, hematoxylin-eosin (HE) staining was conducted. The histological structure of the specimens was evaluated under electron microscopy (BX51T-PHD-J11, Olympus, Tokyo, Japan). Criteria for Mankin's score were as follows: a total score of 0 represented normal cartilage tissue, smooth and flat surface layer, uniform distribution of chondrocytes, and uniform HE staining without loss of staining; a total score of 2-7 represented mild injury, with small fissures in the superficial layer, hypertrophic chondrocytes in the middle and deep layers, and loss of staining in the HE staining; a total score of 8-12 represented moderate injury, with uneven superficial layer, fissures in the middle and deep layers, disorganized arrangement of cells in the middle and deep layers, a large number of clustered chondrocytes, uneven HE staining, and loss of staining in the superficial and middle and deep layers; a total score of 13-14 represented severe injury, with thinning of the superficial layer and deep fissures to the subchondral bone, fissure of subchondral bone, obviously disordered cell arrangement, a large number of clustered chondrocytes, un-uniformed HE staining, and obvious loss of staining in the whole layer.

Gross morphology

The ME. Moran Gross Morphology Scale [13] was used to score the items by naked eye, including five dimensions of mobility (equal to normal limb activity scored 2 points, 50%-100% of normal limb activity scored 1 point, and <50% of normal limb activity scored 0 point), joint adhesion (no adhesion scored 2 points, less adhesion scored 1 point, and more adhesion scored 2 points), injured joint recovery (2 points for complete recovery, 1 point for partial recovery, and 0 point for no recovery), articular cartilage surface (2 points for translucency, 1 point for matte, and 0 point for colorless or irregular), and articular cartilage defect (the articular cartilage defect was completely replaced by normal cartilage tissue as 2 points, replaced by a little cartilage tissue as 1 point, and no improvement as 0 point), with higher scores representing better joint morphology.

Oxidative stress indices

Blood samples were collected from rabbits before intervention, at week 4 and week 12 of CPM intervention, and the levels of superoxide dismutase (SOD) (the applied kit was purchased from Hefei Laier Biotechnology Co., Ltd.) and malondialdehyde (MDA) (the applied kit was purchased from Beijing Solarbio Science & Technology Co., Ltd.) were analyzed by micro-

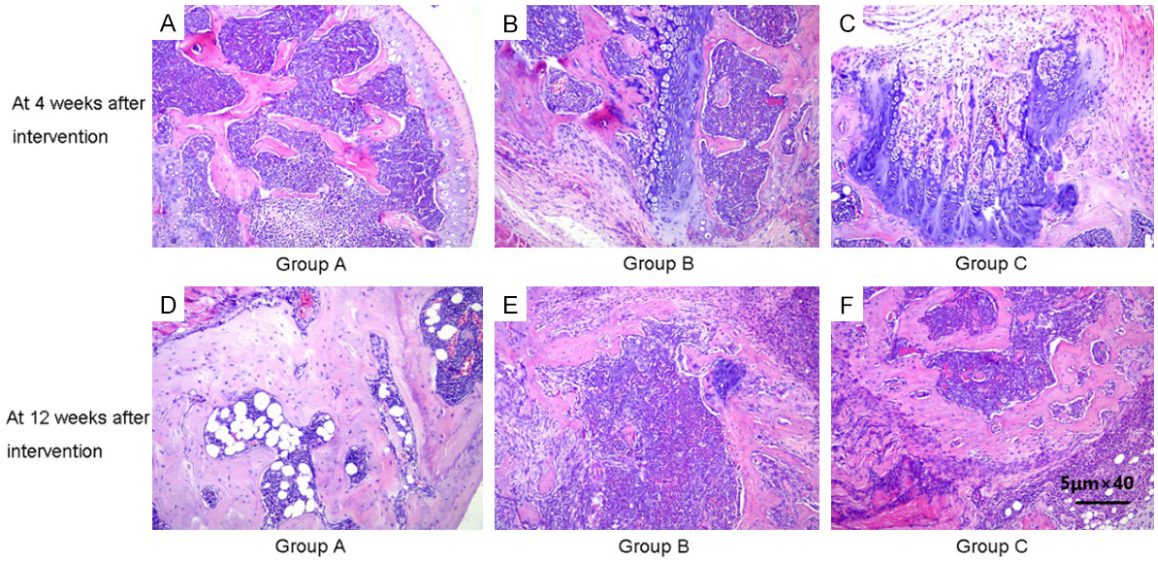

Figure 2. HE staining of knee joint tissues in experimental rabbits. A-C: At 4 weeks after intervention, the staining of knee joint tissues in groups A, B, and C, respectively; D-F: At 12 weeks after intervention, the staining of knee joint tissues in groups A, B, and C, respectively.

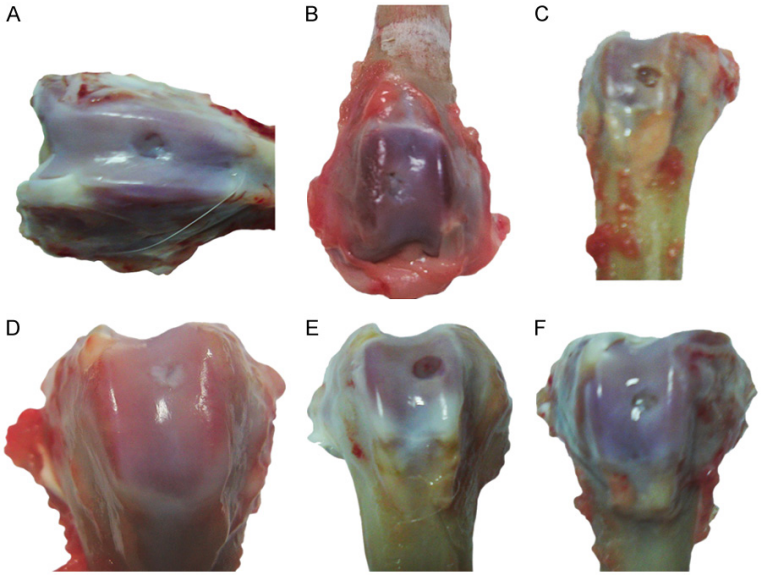

Figure 3. Images of rabbit joints before and after intervention. A-C: At 4 weeks after intervention, the images of knee joint in groups A, B, and C, respectively; D-F: At 12 weeks after intervention, the images of knee joint in groups A, B, and C, respectively.

assay. Each index was tested three consecutive times and the average was taken as the final result.

Statistical methods

SPSS24.0 statistical software was used for data analysis. The Kolmogorov-Smimov test was used to test the normality of the quantitative data. Quantitative data in this study were all subjected to normal distribution, described as mean ± standard deviation (SD), independent-samples t-test (two groups) or ANOVA (three or more groups) were used for inter-group comparison, and post hoc comparisons were analyzed by SNK test. Qualitative data were described as n (%), and the chi-square test was used for inter-group comparison. The difference was considered statistically significant at $P< 0.05$. GraphPad Prism 8.3 was used for figure plotting [14].

Results

Comparison of baseline data

Gender, body mass, and joint flexion were included as baseline data, and a comparison was conducted on the intergroup differences among the three experimental rabbit groups regarding the above information, and the results showed that the differences among the

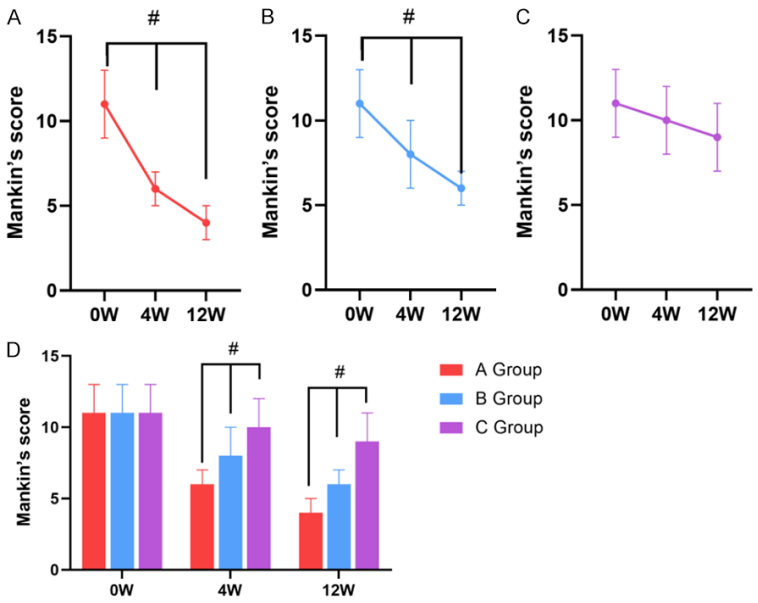

Figure 4. Changes in Mankin's scores. A-C: Changes of Mankin's scores over time in groups A, B, and C, respectively; D: Differences in Mankin's scores among groups A, B and C at different time. #represents statistically significant difference between groups of the same index (P<0.05). n=5 rabbits (10 knees) each group.

three groups regarding the above indicators were not statistically significant (P>0.05), suggesting good comparability (**Table 1**).

Body mass measurements

The body masses of the experimental rabbits were measured before intervention, at week 4 and week 12 of CPM intervention. No significant difference was observed in body weight among the three groups at the above time points (P>0.05) (**Figure 1**).

Mankin's score before and after intervention

The Mankin's score showed no statistically significant difference among the three groups before intervention (P>0.05). In the week 4 of intervention, the Mankin's scores of rabbits in groups A and B were decreased compared with those before intervention (P<0.05), while those in group C were not significant (P>0.05). At the week 12 of intervention, the Mankin's scores in groups A and B were decreased significantly compared with the score at week 4 of intervention (P<0.05), and there was also no significant change in group C (P>0.05). Mankin's scores were the lowest in group A, followed by group B, and the highest in group C (P<0.05) (**Figures 2-4**).

Changes in knee joint gross morphological scores

At week 4 of CPM intervention, the gross morphological scores of the knee joints were the highest in group A, followed by group B, and the lowest in group C (P<0.05). At week 12 of CPM intervention, the gross morphological scores of the knee joints in groups A and B were increased continuously, and the scores were the highest in group A, followed by group B, and the lowest in group C (P<0.05) (**Table 2**; **Figure 5**).

Changes in oxidative stress indices

MDA and SOD levels in the blood samples of the experimental rabbits showed no significant difference before intervention (P>0.05). After 4 weeks of intervention, all the three groups of rabbits showed a decrease in MDA levels and an increase in SOD levels, with the lowest MDA level in group A, followed by group B and the highest in group C (P<0.05). At 12 weeks of intervention, the MDA level was further decreased and the SOD level was increased again, and MDA level was the lowest in group A, followed by group B, and the highest in group C, and the SOD level was the highest in group A, followed by group B, and the lowest in group C (P<0.05) (**Figures 6** and **7**).

Discussion

Epidemiological study shows that KOA is the most common type of arthritis [15, 16]. In recent years, with the aging of society, the incidence of KOA is still increasing [17]. The traditional view is that KOA patients need long-term immobilization, but this often leads to muscle atrophy, joint spasm and intra-articular adhesions, hindering the recovery of joint function and even increasing the risk of joint stiffness [18-20]. Passive exercise can promote the healing of joint cartilage through regular exercise [21]. Several studies indicate that regular passive exercise can help relieve joint pain and

Table 2. Changes in the gross morphological scores of knee joints

Item		CPM Week 4					CPM Week 12				
		A (n=10)	B (n=10)	C (n=10)	F/χ^2	*P*	A (n=10)	B (n=10)	C (n=10)	F/χ^2	*P*
Mobility	Equal to normal limb mobility	9	5	5	5.484	0.241	9	6	6	3.857	0.426
	50%-100% normal limb mobility	1	3	2			1	3	2		
	<50% normal limb mobility	0	2	3			0	1	2		
Joint adhesions	No	9	3	1	14.636	0.006	9	3	2	21.234	<0.001
	Less	1	2	3			1	7	3		
	More	0	5	6			0	0	5		
Injured joint recovery	Complete	5	2	1	13.707	0.008	8	3	1	15.500	0.004
	Part	5	7	3			2	6	4		
	None	0	1	6			0	1	5		
Articular cartilage surface	Translucent	10	7	3	11.700	0.020	10	4	3	17.487	0.002
	No shine	0	2	6			0	5	2		
	Colorless	0	1	1			0	1	5		
Articular cartilage defect	Completely normal	4	2	1	9.824	0.044	9	3	1	14.417	0.006
	Slightly normal	6	7	4			1	3	4		
	None	0	1	5			0	4	5		
Mean score		8.71±1.21[a,b]	5.87±1.24[a]	4.01±0.98	42.421	<0.001	9.16±0.34[a,b]	6.21±0.26[a]	4.19±0.39	558.959	<0.001

Note: Compared with group C, [a]P<0.05, compared with group B, [b]P<0.05.

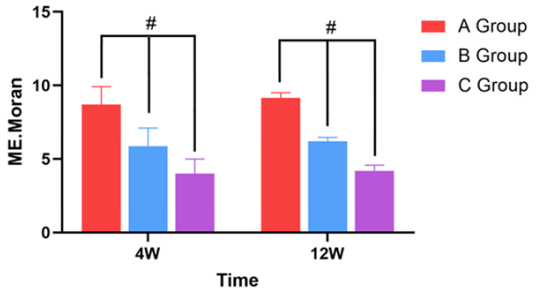

Figure 5. Changes in the gross morphological scores of knee joints in each group. #represents statistically significant difference between groups of the same index. n=5 rabbits (10 knees) each group.

stiffness of KOA patients and improve the range of motion, and the therapeutic effect is better than traditional long-term fixation therapy, suggesting that passive exercise has a theoretical basis in the clinical treatment of KOA [22, 23].

In this study, the effect of CPM on Mankin's score and gross morphology of osteoarthritis of the knee in rabbits was investigated. Compared to group C, the experimental rabbits in groups A and B with 4 weeks of CPM recovered significantly faster in terms of mobility, joint adhesions, cartilage surface, and cartilage defects, suggesting that CPM accelerated knee cartilage repair and eliminated joint inflammation. An animal experimental study [24] indicated that CPM could stimulate the metabolism of chondrocytes to a certain extent and accelerate the synthesis of cartilage mechanistic proteins, thus contributing to the reconstruction of damaged cartilage, reducing intra-articular adhesion, and promoting the elimination of lysosomal enzymes and inflammatory exudates, all of which were similar to the results in this study. Mankin's scores of experimental rabbits in groups A and B were significantly lower than those in group C after intervention, and there was also large difference between groups A and B. The reason may be that CPM could alleviate the inflammatory state of the knee joint in KOA rabbits and accelerate the reconstruction and repair of cartilage tissue.

This study also investigated the mechanism of CPM intervention in improving the symptoms of knee osteoarthritis in KOA rabbits. It was found that the MDA level was decreased and the SOD level was increased in groups A and B after intervention. A controlled experiment conducted on patients with KOA found that free radicals generated by oxidative stress play a vital role in the development of KOA; excessive free radicals could cause oxidative or nitrative damage to a variety of molecules, and then result in the overexpression of MDA and protein hydroxyl, leading to hyaluronic acid depolymerization, reduced synovial fluid viscosity, inactivation of anti-protease and induction of bone resorption, promoting cartilage degradation and ultimately developing KOA [25]. The results in the study suggested that CPM could reduce MDA levels and increase SOD levels in KOA rabbits, and the degree of change was closely related to the intensity of CPM, suggesting that CPM can effectively improve the actual overproduction of oxygen radicals, which may also be one of the crucial reasons why CPM can accelerate the recovery of knee joint function in rabbits modeled with KOA.

The innovation of this study is that the intervention value of CPM in experimental rabbits with knee joint injury was elaborated through animal experiments, which provides theoretical reference for the treatment of patients with similar diseases in clinic. The limitations are as follows: (1) the sample size was small, resulting in a lack of comprehensiveness of the results; (2) the study period was short and the dynamic observation of indicators was absent. In the next step, animal experiments with larger sample size and more intensive observation time points will be carried out to verify the effectiveness of CPM and provide new treatment methods for the follow-up treatment of KOA patients and the improvement of the quality of life of KOA patients. In conclusion, CPM can effectively improve the symptoms of KOA as well as the joint mobility in rabbits, and the analysis of the mechanism may be related to the ability of CPM to reduce the overproduction of peroxides at the lesion.

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Disclosure of conflict of interest

None.

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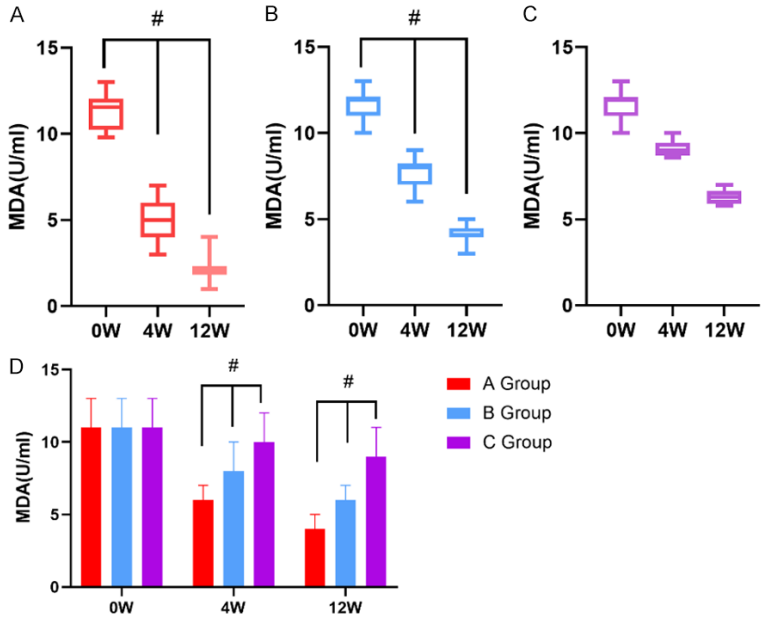

Figure 6. Changes in MDA. A-C: Changes of MDA levels over time in groups A, B, and C, respectively; D: Differences in MDA levels among groups A, B and C at different time. #represents statistically significant difference between groups of the same index (P<0.05). n=5 rabbits (10 knees) each group.

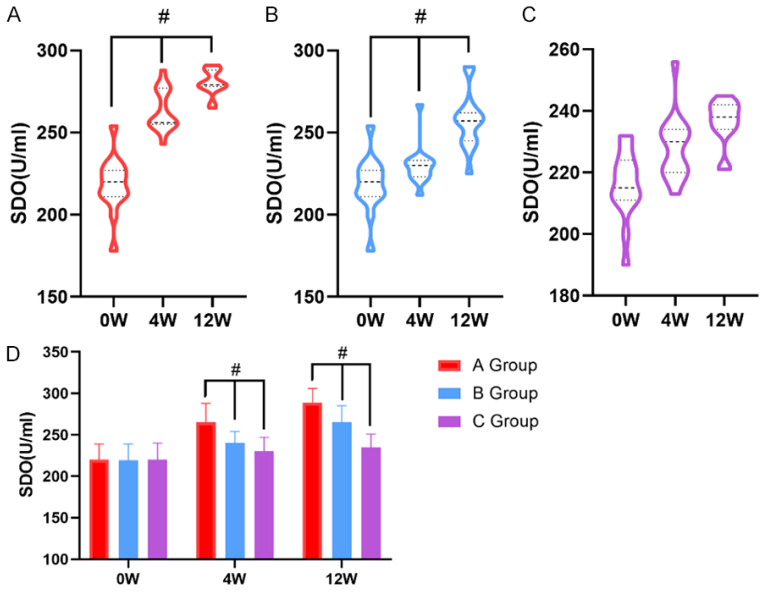

Figure 7. Changes in SOD before and after intervention. A-C: Changes of SOD levels over time in groups A, B, and C, respectively; D: Differences in SOD levels among groups A, B and C at different time. #represents statistically significant difference between groups of the same index (P<0.05). n=5 rabbits (10 knees) each group.

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