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Original Article

Effect of extracorporeal shock wave treatment combined with rehabilitation therapy on early and middle stage knee osteoarthritis

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Abstract: Objective: We aimed to explore the effect of extracorporeal shock wave treatment (ESWT) combined with rehabilitation therapy (RT) on the improvement of collagen 2-1 (Coll2-1) and cartilage oligomeric matrix protein (COMP) in patients with early and middle stage knee osteoarthritis (KOA). Methods: The clinical data of 109 patients diagnosed with early and middle stage KOA in our hospital were collected retrospectively. According to different treatment methods, they were divided into Group A (GA) (n=54) injected with sodium hyaluronate (SH) into the articular cavity, and Group B (GB) (n=55) treated with ESWT combined with RT in addition to treatment of GA; so as to compare their surface electromyography (sEMG) of quadriceps femoris, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analogue scale (VAS) scores and Lysholm knee function scores before and after treatment. At the same time, the levels of COMP and Coll2-1 in the joint fluid were tested through enzyme linked immunosorbent assay (ELISA) in both groups. Results: The median frequency (MF) and mean power frequency (MPF) at 60°s^{-1} and 180°s^{-1} showed no obvious attenuation after treatment in GB (P>0.05) but did show obvious attenuation after treatment in GA (P<0.05). WOMAC of GB was lower than that of GA after treatment (P<0.05). VAS scores of GB were lower than those of GA after treatment (P<0.05). Lysholm knee function scores of GB were higher than those of GA after treatment (P<0.05). The levels of COMP and Coll2-1 in GB were lower than those in GA after treatment (P<0.05). Conclusion: ESWT combined with RT can reduce the levels of COMP and Coll2-1, improve the knee function and alleviate the pain of patients with early and middle stage KOA.

Keywords: Early and middle stages, knee osteoarthritis, extracorporeal shock wave, rehabilitation therapy, effect

Introduction

KOA is a common degenerative joint disease causing a series of pathological changes, including joint synovitis, proliferation of osteophyte, subchondral sclerosis and cartilage wear, etc., due to such factors as joint deformity, congenital joint anomaly, trauma, strain, obesity and age, etc. [1, 2]. Its clinical manifestations include late joint deformity, limited joint motion, swelling and pain, etc. So it is also known as hypertrophic arthritis, senescent arthritis, degenerative arthritis and osteoarthrosis [3].

Operations are one of the most common methods to treat KOA in clinical practice. In addition to an operation, scientific and reasonable rehabilitation measures are also important to maintain therapeutic effects, and the rehabilitation methods usually include acupuncture, physiotherapy and exercise, etc. [4, 5]. Besides, ESWT is also an important method to treat early and middle stage KOA in clinical practice [6]. This treatment method can not only alleviate the pain of patients, but also inhibit the cartilage degeneration and thus promote subchondral bone remodeling [7]. Animal experiments also showed that this method can regulate the expression of cell and inflammatory factors in the joint fluid. Collagen Type II is a major structural composition of cartilage tissues and its degradation products in blood are closely correlative with the progression of joint injury in osteoarthritis [8]. Coll2-1, is a biomarker of collagen degradation, which can not only be applied to drug development, but also be used to evaluate the therapeutic response of pa-

tients [9]. According to researche, Coll2-1 can be used as one of the important factors to predict the therapeutic response of osteoarthritis [10]. COMP, is one of the potential biomarkers for KOA, as it can respond to the disease course of KOA and be used as one of the key indexes to evaluate therapeutic effect [11].

In view of this, in order to alleviate the pain of patients with early and middle stage KOA, and improve the joint function and enhance the therapeutic effect; ESWT combined with RT was used in this study to achieve an ideal rehabilitation effect.

Material and methods

Materials

The clinical data of 109 patients diagnosed with early and middle stage KOA in our hospital were collected retrospectively. According to different treatment methods, these patients were divided into GA (n=54) injected with SH into the articular cavity and GB (n=55) treated with ESWT combined with RT in addition to treatment in GA. (1) Inclusion criteria: The patients were informed about and agreed with participating in this study, and written informed consent was provided. They were aged over 45 years old. This studies qualifications met the diagnostic criteria of osteoarthritis formulated by Chinese Orthopaedic Association [12] and was approved by the Medical Ethics Committee of our hospital. The affected area was unilateral knee joint. (2) Exclusion criteria: This study excluded patients who quit midway; those with bilateral knee osteoarthritis; those aged over 70 years old; those with severe blood disease and cardiovascular disease; those with secondary osteoarthritis; those with meniscus injury; and those with fracture of the knee joint.

Methods

GA: Patients were kept in the supine position with the affected knee joint exposed completely. The puncture point was located at the intersection of upper edge and outer edge of patella. The needle was inserted, inwards and downwards, into the joint space of the patella at an angle of 45°. Twenty mg Sodium Hyaluronate Injection (manufacturer: Shanghai Haohai Biological Technology Co., Ltd.; approval number: SFDA approval number H20051837; specification: 2 ml: 20 mg) was injected slowly in the case of no injection resistance and no bleeding. If there was a large amount of knee joint hydrops, the joint fluid was extracted first and the drug was injected thereafter. After injection, patients massaged and kneaded the patella gently and moved the joint to promote drug diffusion and absorption. The treatment was performed once a week and the public treatment was performed four times a week.

GB: Patients were treated with ESWT combined with RT in addition to treatment of GA. (1) ESWT: The shock point was the location of the pain while passively pulling the ligaments of the knee joint at affected side, the pain location while flexing and extending the joint, and the tenderness point surrounding the affected knee joint. The treatment instrument was MASTERPULS MP100 ESWT apparatus manufactured by STORZ MEDICAL AG, with treatment pressure of 3 bar, energy flux density of 0.1 mJ/mm^2 and shock frequency of 10 Hz. The shock was performed 2,000 times in each location. The treatment was performed once a week for a succession of 4 treatment times. (2) RT: Patients carried out the range of motion (ROM) training according to guidance. ROM was determined based on the severity of disease, generally starting from 0° which was raised by 1° every 20 min to the angle where the patients was able to make active movements. The training lasted for 1.5 h at a time and was performed twice a day. After the training for 7 d, the ROM of both knee joints was over 90°. When the patients performed flexion and extension strength training, they were kept in the supine position on a flat bed with their knee joints straight. Then the quadriceps femoris was tightened for 10 s and relaxed for 5 s. This training was performed 20 times per set and 3 sets a day. Then the patients were guided to sit on a chair to perform the flexion and extension training of knee joints. This training was performed 20 times per set and 3 sets a day. The next step was resistance training. The patients sat on a chair, with rubber rings respectively placed on the chair and the ankle joint of affected limb. Then, they were guided to extend the knee joint away from the chair. This training was performed 20 times per set and 3 sets a day.

Observation targets

sEMG test of quadriceps femoris: The sEMG of quadriceps femoris was tested in the affected

Table 1. Comparison of general material between two groups [n (%)]/($\bar{x}$ ± s)

Material		GA (n=54)	GB (n=55)	t/X^2	*P*
Gender (number of cases)	Male	33 (61.11)	35 (63.64)	0.074	0.786
	Female	21 (38.89)	20 (36.36)		
Age (years old)		58.96±1.28	58.99±1.32	0.120	0.904
Disease course (years)		3.28±0.18	3.22±0.22	1.557	0.123
Kellgren-Lawrence grading (number of cases)					
Grade II		41 (75.93)	43 (78.18)	0.079	0.779
Grade III		13 (24.07)	12 (21.82)		

limb respectively before and after treatment. MPF and MF were tested respectively at 60°s^{-1} and 180°s^{-1} [13].

WOMAC: WOMAC was used to evaluate the knee function and symptoms of two groups before and after treatment, including joint function, stiffness and pain. The lower the scores, the better the knee function and the milder the symptoms [14].

VAS scores: VAS was used to evaluate the pain of two groups before and 6 months after treatment. The scores ranged from 0 to 10, with 0 representing no pain and 10 as acute pain. The higher the scores, the more sever the pain [15].

Lysholm knee function scores: The knee function of the two groups was evaluated based on Lysholm knee function scores. There were 34 items with a total of 100 points. The higher the scores, the better the knee function [16].

Levels of COMP and Coll2-1: One ml synovial fluid was extracted from both groups in strict accordance with aseptic technique before and after treatment; then centrifugalization of the samples at 3,000 r/min for 10 min to obtain the supernatant which was put into EP tubes and stored in freezer at -80°C. Levels of COMP and Coll2-1 were tested through ELISA, strictly according to kit instructions. The kit was provided by Beijing Yike Biotechnology Co., Ltd.

Statistical methods

SPSS 22.0 was used for data analysis. The measurement data were represented by mean ± standard deviation. *t* test was used for data in conformity with a normal distribution and Mann-Whitney U test was used for data not in conformity with a normal distribution. The enumeration data were represented by [n (%)] and compared between groups trough chi-squared test. *P*<0.05 represented a statistically significant difference.

Results

Comparison of general materials between the two groups

There were 33 male patients and 21 females in GA, respectively accounting for 61.11% and 38.89%; and 35 males and 20 females in GB, respectively accounting for 63.64% and 56.36%. Patients in GA were aged 50-68 years old, with an average age of (58.96±1.28); and those of GB were aged 51-69 years old, with an average age of (58.99±1.32). The disease course was 2-5 years in GA and 1-4 years in GB, with average values of (3.28±0.18) and (3.22± 0.22), respectively. A total of 41 patients were in Kellgren-Lawrence Grade II and 13 were in Grade III in GA, respectively accounting for 75.93% and 24.07%; and 43 patients were in Grade II and 12 were in Grade III in GB, respectively accounting for 78.18% and 21.82%. There was no statistical difference in gender, age, disease course and Kellgren-Lawrence grading between the two groups (*P*>0.05) (**Table 1**).

Comparison on sEMG of quadriceps femoris at 60°s^{-1} between the two groups

MF and MPF at 60°s^{-1} were respectively (0.55± 0.15) and (0.66±0.12) in GA and (0.56±0.12) and (0.68±0.09) in GB before treatment, showing no obvious difference (*P*>0.05). MF and MPF at 60°s^{-1} were respectively (0.55±0.11) and (0.66±0.02) in GB after treatment, which was higher than (0.42±0.05) and (0.58±0.01) in GA (*P*<0.05). There was no obvious attenuation in MF and MPF of GB at 60°s^{-1} after treat-

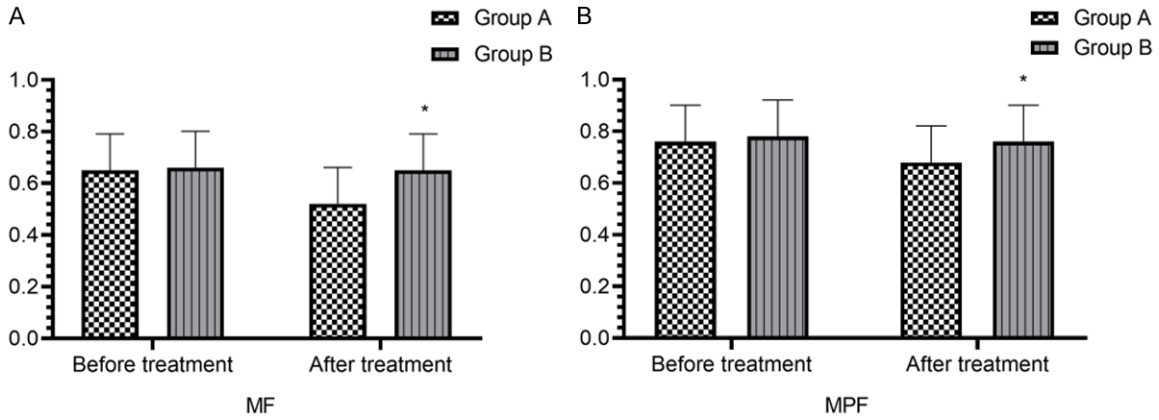

Figure 1. Comparison on sEMG of quadriceps femoris at 60°s^{-1} between two groups. *P*>0.05 meant the comparison of MF and MPF at 60°s^{-1} between two groups before treatment. MF and MPF of GB at 60°s^{-1} were higher than those of GA after treatment (*P*<0.05). *meant *P*<0.05 in comparison with GA.

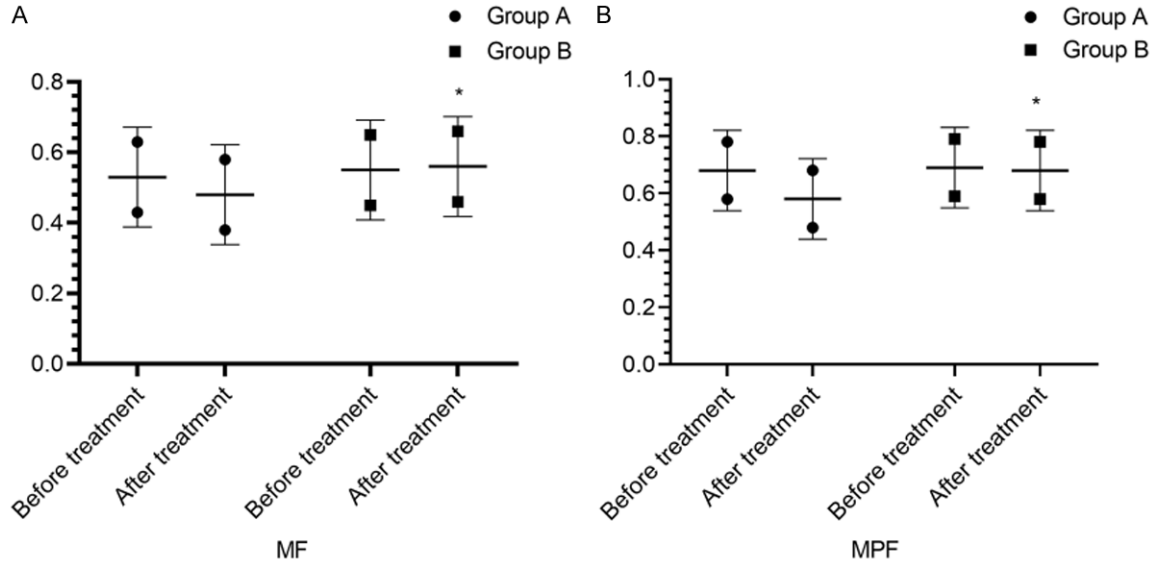

Figure 2. Comparison on sEMG of quadriceps femoris at 180°s^{-1} between two groups. *P*>0.05 meant the comparison of MF and MPF at 180°s^{-1} between two groups before treatment. MF and MPF of GB at 180°s^{-1} were higher than those of GA after treatment (*P*<0.05). *meant *P*<0.05 in comparison with GA.

ment; but there was obvious attenuation in MF and MPF of GA at 60°s^{-1} after treatment (*P*<0.05) (**Figure 1**).

Comparison on sEMG of quadriceps femoris at 180°s^{-1} between two groups

MF and MPF at 180°s^{-1} were respectively (0.43±0.09) and (0.58±0.18) in GA and (0.45±0.08) and (0.59±0.17) in GB before treatment, showing no obvious difference (*P*>0.05). MF and MPF at 180°s^{-1} were respectively (0.46±0.12) and (0.58±0.15) in GB after treatment, higher than (0.38±0.02) and (0.48±0.01) in GA (*P*<0.05). There was no obvious attenuation in MF and MPF of GB at 180°s^{-1} after treatment; but there was an obvious attenuation in MF and MPF of GA at 180°s^{-1} after treatment (*P*<0.05) (**Figure 2**).

Comparison of WOMAC between two groups

There was no obvious difference in WOMAC scores between the two groups before treatment (*P*>0.05). WOMAC in both groups reduced after treatment (*P*<0.05). WOMAC in GB was lower than that of GA after treatment (*P*<0.05) (**Table 2**).

Table 2. Comparison of WOMAC between two groups ($\bar{x} \pm s$)

Group	Before treatment	After treatment
GA (n=54)	70.12±5.63	38.96±2.27#
GB (n=55)	70.19±5.61	25.12±1.18#,*
t	0.065	40.042
P	0.948	0.000

Note: #meant *P*<0.05 in comparison with the results before treatment; and *meant *P*<0.05 in comparison with GA.

Table 3. Comparison of VAS scores between two groups ($\bar{x} \pm s$, scores)

Group	Before treatment	After treatment
GA (n=54)	7.25±0.58	3.68±.0.39#
GB (n=55)	7.29±0.56	1.02±0.18#,*
t	0.366	45.855
P	0.715	0.000

Note: #meant *P*<0.05 in comparison with the results before treatment; and *meant *P*<0.05 in comparison with GA.

Table 4. Comparison of Lysholm knee function scores between two groups ($\bar{x} \pm s$, scores)

Group	Before treatment	After treatment
GA (n=54)	45.25±2.36	62.52±3.68#
GB (n=55)	45.29±2.29	80.15±5.62#,*
t	0.090	19.338
P	0.929	0.000

Note: #meant *P*<0.05 in comparison with the results before treatment; and *meant *P*<0.05 in comparison with GA.

Comparison of VAS scores between the two groups

There was no obvious difference in VAS scores between the two groups before treatment (*P*>0.05). VAS scores of both groups reduced after treatment (*P*<0.05). VAS scores of GB were lower than those of GA after treatment (*P*<0.05) (**Table 3**).

Comparison of Lysholm knee function scores between the two groups

There was no obvious difference in Lysholm knee function scores between two groups before treatment (*P*>0.05). Lysholm knee function scores of both groups increased after treatment (*P*<0.05). Lysholm knee function scores of GB were higher than those of GA after treatment (*P*<0.05) (**Table 4**).

Comparison of COMP level between the two groups

COMP was (5.32±0.88) μg/ml in GA and (5.36±0.82) μg/ml in GB before treatment, showing no obvious difference (*P*>0.05). COMP was (4.02±0.38) μg/ml in GB after treatment, lower than (4.85±0.49) μg/ml in GA (*P*<0.05) (**Figure 3**).

Comparison of Coll2-1 level between the two groups

Coll2-1 was (173.56±12.28) nmol/L in GA and (173.69±12.15) nmol/L in GB before treatment, showing no obvious difference (*P*>0.05). Coll2-1 was (110.02±5.52) nmol/L in GB after treatment, lower than (135.69±8.55) nmol/L in GA (*P*<0.05) (**Figure 4**).

Analysis of X-ray imaging features between two groups

The anterior and lateral radiographs of the knee joint of GA before treatment showed that the margins of the constituent bones of the right knee joint became sharp and dense; the intercondylar crest was intumescent; the medial space of the knee joint was narrowed; the joint relationship was normal; the suprapatellar bursa was widened; the density was increased; and the surrounding soft tissue was slightly swollen. The anterior and lateral radiographs of the knee joint of GB before treatment showed that slight labial hyperplasia was observed at the bone margins of both knee joints; the bilateral intercondylar prominence became sharp; the knee joint space was slightly narrowed; the soft tissue layers of both knees were clear, and no abnormal density lesions were observed (**Figure 5**).

Discussion

KOA is an orthopedic disease based on degenerative changes and also one of the key causes for leg pain in middle-aged and senior people who are the main population with this disease [17, 18].

At present, no specific treatment has been found to successfully treat early and middle

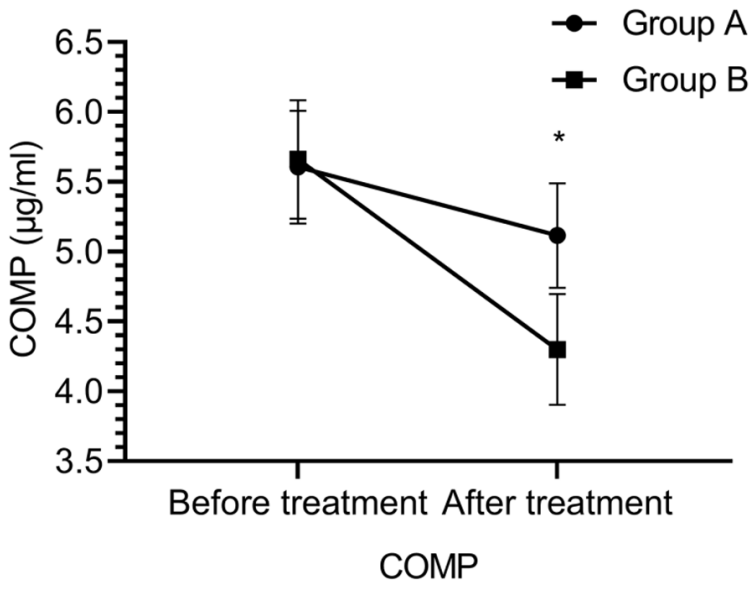

Figure 3. Comparison of COMP level before and after treatment between two groups. *P*>0.05 meant the comparison of COMP level between two groups before treatment. The COMP level of GB was lower than that of GA after treatment (*P*<0.05). *meant *P*<0.05 in comparison with GA.

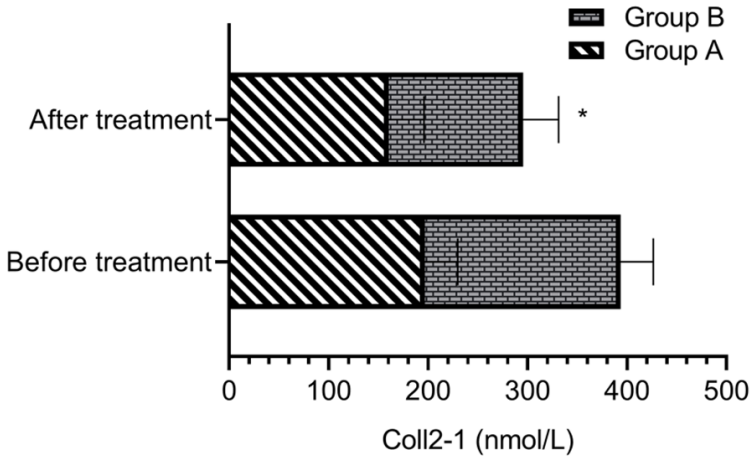

Figure 4. Comparison of CollI2-1 level before and after treatment between two groups. *P*>0.05 meant the comparison of CollI2-1 level between two groups before treatment. The CollI2-1 level of GB was lower than that of GA after treatment (*P*<0.05). *meant *P*<0.05 in comparison with GA.

stage KOA in clinical practice and non-steroidal anti-inflammatory drugs are usually used for its basic treatment. However, the long-term medication will inhibit cartilage synthesis and damage cartilage cells and thus aggravate the disease. So these drugs are limited to a certain extent in clinical application [19, 20]. SH is an important part of articular cartilage and synovial fluid. It can improve the mechanical lubrication of joints through exogenous supplementation of synovial fluid and repair the damaged physiological barrier to avoid the pain caused by friction of articular cartilage, alleviate the clinical symptoms and improve the ROM [21]. Meanwhile, Sodium Hyaluronate Injection can effectively combine the glycoprotein in synovial fluid to block the inflammatory response, inhibit WBC migration, reduce intra-articular effusion, promote the synthesis of glycoprotein and chondroitin sulfate, repair cartilage and decrease the sensitivity to pain [22, 23]. In spite of a certain therapeutic effect achieved through this drug treatment in early and middle stage KOA, ESWT was combined with RT in this study to further recover the knee function and alleviate the pain [24]. In this study, there was no obvious attenuation in MF and MPF of GB at $60°s^{-1}$ and $180°s^{-1}$ after treatment, but obvious attenuation in MF and MPF of GA. This implied that ESWT combined with RT in addition to SH could strengthen the strength of quadriceps femoris and increase the fatigue endurance of the muscle. Next, WOMAC and VAS scores of GB reduced and Lysholm knee function scores increased after treatment (*P*<0.05), which further proved the effectiveness of combination therapy. As for the exploration of its mechanism of action, ESWT is a non-invasive treatment. It can reduce the sensitivity of peripheral nerves, enhance the pain threshold, inhibit the pain information transmission, and achieve an obvious analgesic effect in many skeletal muscle diseases. Then, the release of inflammatory factors is inhibited in cartilage cells to promote the expression of such cell factors as vascular endothelial growth factor, bone morphogenetic protein and basic fibroblast growth factor, etc., which can improve cartilage metabolism and

Figure 5. Analysis of X-ray imaging features between two groups. A: The anterior and lateral radiographs of the knee joint of GA before treatment showed that the margins of the constituent bones of the right knee joint became sharp and dense; the intercondylar crest was intumescent; the medial space of the knee joint was narrowed; the joint relationship was normal; the suprapatellar bursa was widened; the density was increased; and the surrounding soft tissue was slightly swollen. B: The anterior and lateral radiographs of the knee joint of GB before treatment showed that slight labial hyperplasia was observed at the bone margins of both knee joints; the bilateral intercondylar prominence became sharp; the knee joint space was slightly narrowed; the soft tissue layers of both knees were clear, and no abnormal density lesions were observed.

promote cartilage cell differentiation and proliferation and cartilage repair [25]. After absorbing the energy from bone absorption in impact therapy, new microfractures will be formed to promote osteogenesis, avoid bone cysts and intensify joint bearing capacity. Additionally, in the process of systematic rehabilitation exercise, the synovium of the joint is stimulated continually to secrete hyaluronic acid and lubricate the articular cavity. Rehabilitation exercise can also strengthen the muscle endurance and strength surrounding joints and thus enhance the stability of joints. In this process, joint contracture can be improved to avoid ankylosis and improve disuse atrophy [26].

This study also showed that the levels of COMP and Coll2-1 of GB were lower than those of GA after treatment ($P<0.05$). This implied that ESWT combined with RT further alleviated KOA and recovered joint function. Liu et al. [27] also found that the COMP level and Coll2-1 level in the observation group were lower than those in the control group after treatment ($P<0.05$), which was highly consistent with the results of this study. To explore its mechanism of action, COMP is a tissue specific matrix protein for synthesis and secretion of cartilage cells. It is abundant in hyaline cartilage and also exists in synovial fluid and blood. This protein can not only stabilize the collagen network, but also effectively maintain the joint stability and physiological function of articular cartilage. The content change of COMP can be used to predict the condition of KOA patients to a certain extent, so it is one of the biomarkers for KOA used in clinical practice [28]. Coll2-1 is a degradation product of Collagen Type II, showing obviously higher concentrations in synovial fluid and blood of osteoarthritis patients. Clinically, the oxidation-related cartilage degradation can be monitored through Coll2-1 to judge the influence of antioxidative or anti-inflammatory drugs on cartilage degradation [29]. In this study, the levels of COMP and Coll2-1 in GB were lower than those in GA after treatment. This implied that ESWT combined with RT achieved a better effect in treatment of early and middle KOA.

In conclusion, ESWT combined with RT can reduce the levels of COMP and Coll2-1, improve the knee function and alleviate the pain of patients with early and middle stage KOA.

In spite of some achievements, this study had the limitation of a small sample size. So a more comprehensive and longer term research with larger sample size shall be carried out in the future.

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Disclosure of conflict of interest

None.

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