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Original Article

Clinical effect of acupuncture combined with basic treatment on knee osteoarthritis and influence on inflammatory mediators

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ABSTRACT

Objectives: The study aims to investigate the curative efficacy of acupuncture on knee osteoarthritis (KOA) and its improvement on related scores and blood indexes.

Patients and methods: This study conducted between January 2023 to June 2023, 108 KOA patients (48 males and 60 females; mean age: 61.0±6.8 years; range 43 to 79 years) were randomly divided into the control group and research group. Both groups received basic treatment, including adequate rest and exercise, and oral celecoxib capsules. The research group performed acupuncture operations on the inner knee eye (EX-LE4), outer knee eye (EX-LE5), Yanglingquan (GB34), and Zusanli (ST36). In the control group, three nonacupuncture points were determined for sham acupuncture. The level of Michel Lequesne index of severity for osteoarthritis score, Visual Analog Scale, Lysholm Knee Score Scale, erythrocyte sedimentation rate, C-reactive protein, interleukin (IL)-1β, IL-6, transforming growth factor-beta (TGF-β), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), and p38 mitogen-activated protein kinase (p38 MAPK) were compared before and after treatment.

Results: The reduction of inflammatory markers in the research group was greater than that in the control group after treatment. The levels of cytokines TGF-β, IGF-1, and FGF-2 were significantly increased after treatment, and the levels in the research group were higher than those in the control group during the same period. In addition, p38 MAPK messenger ribonucleic acid (mRNA) was significantly downregulated after treatment, and the level in the research group was lower than that in the control group during the same period.

Conclusion: Acupuncture combined with basic treatment can effectively promote the relief of symptoms and the improvement of knee joint function and effectively inhibit the expression of the p38 MAPK signaling pathway.

Keywords: Acupuncture, inflammation, knee osteoarthritis, p38 MAPK signaling pathway.

Knee osteoarthritis (KOA) is an usual degenerative disease of the knee joint in middle-aged and elderly people.[1] At the time of onset, the symptoms are mild, only with joint pain and obvious discomfort. When the symptoms are severe, the patient can develop into disability, which will not only greatly affect the mental health and quality of life of patients but also greatly increase the economic burden of patients. The coming of the aging society will greatly increase the incidence of KOA, and the impact on medical treatment and society cannot be ignored.[2] At present, the clinical treatment of KOA is mainly conservative, including active exercise recovery and the use of nonsteroidal anti-inflammatory drugs. However, the long-term use of exercise therapy is a challenge for most patients, and the gastrointestinal reaction and kidney damage of nonsteroidal anti-inflammatory drugs also limit the long-term use of these drugs.[3] In addition, total knee replacement is also a surgical treatment for KOA patients if necessary. Nonetheless, given the high risk of surgery and the additional cost of treatment, finding new treatments remains an extremely important priority for this research.

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Acupuncture has a long history and has been practiced in China for more than 2,500 years, being used to treat various types of chronic pain. Clinical studies have shown that acupuncture has a better long-term effect on KOA than operative treatment and has few side effects on the body.[4,5] In recent years, many studies at home and abroad have reported the exact efficacy of acupuncture in relieving joint pain and promoting joint function recovery in patients with KOA.[6-8] A prospective randomized controlled clinical trial showed that acupuncture treatment was similar to physical therapy in pain relief and functional improvement in KOA and did not differ significantly.[9] An updated meta-analysis showed that acupuncture therapy was superior to the pharmacotherapy group in alleviating pain in KOA in the short term and in the long term.[6] The updated 2019 American College of Rheumatology (ACR) evidence-based guidelines for the comprehensive treatment of osteoarthritis recommend the use of acupuncture for OA patients.[10]

Studies have shown that the early and progressive stages of KOA are often accompanied by inflammation and are associated with cartilage degeneration and defects.[11] Some inflammatory factors, such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), can be detected in early KOA, indicating that inflammatory factors are associated with the occurrence and development of KOA. Moreover, since cartilage lesions can easily lead to osteoarthritis, changes in the levels of some growth factors related to cartilage formation, such as transforming growth factor-beta (TGF-β), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor-2 (FGF-2), also affect the occurrence and development of KOA.[12,13] The p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway has been shown to be associated with inflammation.[14] Wei et al.[15] reported that inhibition of the p38 MAPK signaling pathway is associated with delayed progression of KOA. Wang et al.[16] pointed out that electroacupuncture could significantly inhibit the activation of p38 MAPK and improve the inflammatory response of 2,4-dinitrofluorobenzene induced contact dermatitis in rats. In addition, p38 MAPK signaling pathway plays a key role in cartilage injury and apoptosis.[17,18] Therefore, based on the above study, 104 patients with KOA were treated with acupuncture and sham acupuncture combined with basic treatment. By evaluating the therapeutic effect, the differences in cytokines, inflammatory factors, and p38 MAPK signaling pathway before and after treatment, we aimed to provide more valuable data reference for clinical practice.

PATIENTS AND METHODS

This study was conducted at the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine with 108 KOA patients (48 males and 60 females; mean age: 61.0±6.8 years; range 43 to 79 years) between January 2023 to June 2023. The diagnosis of KOA was based on the clinical standards of the ACR.[19] Inclusion criteria were as follows: *(i)* knee pain that occurred within the last month; *(ii)* osteophyte formation in radiographs; *(iii)* the joint fluid test meeting the OA standard; *(iv)* morning stiffness ≤30 min; *(v)* bony fricatives; *(vi)* unilateral KOA; *(vii)* Kellgren-Lawrence (K-L) grades of II and III. Exclusion criteria were as follows: *(i)* presence of other rheumatic diseases, such as gouty arthritis, and rheumatoid arthritis; *(ii)* previous history of knee surgery; *(iii)* mental disorders; *(iv)* Coagulation disorders or immune dysfunction; *(v)* malignant tumors; *(vi)* significant cardiovascular and cerebrovascular diseases. A written informed consent was obtained from each patient. The study protocol was approved by the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine Ethics Committee (date: 26.02.2020, no: 2020031). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were randomly grouped into the control group (n=54) and the research group (n=54) based on a list of computer-generated random numbers, which were placed in opaque sealed envelopes. The control group received basic treatment plus sham acupuncture treatment, and the research group received basic treatment plus acupuncture treatment.

Basic treatment refers to teaching and counseling KOA patients and reminding them to keep their joints warm in daily life. Obese people were advised to properly exercise relevant functions after losing weight, minimize weight-bearing activities and strenuous exercise, with the help of walking sticks when necessary, and wear professional knee pads to protect the knee joint. At the same time, each patient was given 200 mg/day celecoxib capsules

(Jiangsu Hengrui Pharmaceuticals Co., Ltd., Jiangsu, China) orally once a day, with warm water after meals. The basic treatment period was four weeks.

Acupuncture treatment is carried out according to the acupoints determined after diagnosis and treatment of traditional Chinese medicine syndrome differentiation. The following acupoints were used in this study: inner knee eye (EX-LE4), outer knee eye (EX-LE5), Yanglingquan (GB34), and Zusanli (ST36). The patient was seated with the knees bent and the knee joint at 90°. After routine disinfection of the acupoints, a sterile needle was used to acupuncture the acupoints. The depth of the needles was about 0.5-1.0 cun (cun is a unit of length developed in ancient China; 1 cun is approximately the width of the patient's own thumb knuckle). After Deqi (Deqi is a sensation that refers to the skin tension around the needle felt by the doctors during the acupuncture process, as well as numbness and sore swelling at the acupoint), a small range of lifting and thrusting twist was performed, and the needles were removed 30 min later. Acupuncture was performed once a day in the morning and six times a week for four weeks.

Sham acupuncture treatment refers to the selection of nonacupoints close to acupoints and shallow injection of sterile needles into the skin. The sham acupuncture group did not need to obtain Deqi in the process of acupuncture, nor did they need to twist or lift the needles. The locations of acupoints and nonacupoints are shown in Table 1.

The Michel Lequesne index of severity for osteoarthritis (ISOA) score,[20] Visual Analog Scale (VAS),[21] and Lysholm Knee Scoring Scale (LKSS)[22] were used to evaluate the changes in knee function in the two groups before and four weeks of treatment, respectively. The ISOA score was evaluated for pain and discomfort, walking ability, and involvement degree of daily life. A total score of 1 to 4 is mild, 5 to 7 is moderate, 8 to 10 is severe, 11 to 13 is very severe, and ≥14 is extremely severe. Pain was rated with VAS on a scale of 0 to 10, with higher scores indicating more severe pain. The LKSS includes eight different items: pain, instability, lock-in, swelling, lameness, stair climbing, squatting, and use of support. The maximum score is 100, with higher scores indicating less disability.

Fasting venous blood of patients was collected before treatment and four weeks after treatment, and various indexes of patients were detected by an automatic biochemical analyzer. The serum was isolated from whole blood after centrifugation, and the following indexes were detected: C-reactive protein (CRP), IL-1β, IL-6, TGF-β, IGF-1, and FGF-2. The erythrocyte sedimentation rate (ESR) was detected by an automatic ESR analyzer. Elevated levels of the proinflammatory cytokines IL-1β and IL-6 indicate inflammation in the body and that an inflammatory response is activated. C-reactive protein is an acute-phase protein synthesized by liver cells when the body is subjected to inflammatory stimuli, such as microbial invasion

TABLE 1
Locations of acupoints and nonacupoints

Description	International code	Locations
		Acupoints
Inner knee eye	EX-LE4	Located in the depression outside the patella and patellar ligament when the knee is bent 90 degrees.
Outer knee eye	EX-LE5	Located in the depression inside the patella and patellar ligament when the knee is bent 90 degrees.
Yanglingquan	GB34	On the outside of the calf, in the depression of the anterior and inferior fibula head.
Zusanli	ST36	It is exactly 3 cun* below EX-LE4.
		Non-acupoints
Point 1	-	Replace EX-LE4. Located on the non-acupoint 1 cun* below EX-LE4.
Point 2	-	Replace GB34. Located on the non-acupoint 0.5 cun* behind GB34.
Point 3	-	Replace ST36. Located on the non-acupoint 3 cun* behind ST36.

* Cun is a unit of length. The cun described in Chinese medicine is a method of determining the location of acupoints based on the patient's own fingers. Due to individual differences, 1 cun is equivalent to the width of a patient's thumb knuckle.

or tissue damage. In addition, patients with acute inflammation tend to have an increased ESR, which could be determined when the patient's ESR was >20 mm/h. The expression of p38 MAPK messenger ribonucleic acid (mRNA) was detected by quantitative real-time (qRT)-polymerase chain reaction (PCR). Total RNA in the serum was extracted for reverse transcription, and the complementary deoxyribonucleic acid (cDNA) obtained by reverse transcription was amplified for the PCR reaction. The reaction conditions were as follows: predenaturation at 95°C for 1 min, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing at 60°C for 15 sec, and extension at 72°C for 20 sec. Beta-actin was set as the internal parameter.

The criterion of curative effect was knee pain disappearing or almost disappearing and the affected joint being able to move freely. Significant relief of knee pain with occasional mild pain or limited mobility was considered markedly effective. Knee joint pain relief with still some pain and limited activity was considered effective. No improvement in pain or mobility restriction was considered ineffective. Total effective rate was calculated with the following formula: [(number of clinical control cases + number of markedly effective cases + number of effective cases) / total number of cases] × 100.

Statistical analysis

The IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA) was used for data analysis. The normality of the quantitative data was assessed using the Kolmogorov-Smirnov test. Data conforming to the normal distribution were expressed as mean ± standard deviation. The paired t-test was used for comparison of differences within groups, and the independent sample t-test was used for comparison of differences between groups. Qualitative data were expressed as frequency (%), and the chi-square test was used to compare the two groups. The G*Power version 3.1.3 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used to calculate the sample size. Considering a 95% confidence interval and 80% power, the minimum sample size was determined to be 108 cases, with 32 cases in the study group and 32 cases in the control group, according to a one-to-one ratio. A p-value <0.05 was considered statistically significant.

RESULTS

Comparison of baseline data

Baseline data of subjects in the two groups are collected in Table 2. There was no significant difference in age, sex ratio, body mass index, duration of disease, and location of injury between the two groups, which was of comparable value (p>0.05).

Comparison of knee function scores, laboratory biochemical indexes, and p38 MAPK protein levels before and after treatment

As shown in Table 3, there was no significant difference in Michel Lequesne (score) between the two groups before treatment. After treatment, the scores of both groups were significantly lower than those before treatment (p<0.001). After treatment, the Michel Lequesne score in the research group was lower than that in the control group (p<0.01). The VAS

TABLE 2
Basic clinical information statistics of the subjects

	Control group (n=54)		Research group (n=54)		
Items	n	Mean±SD	n	Mean±SD	p
Age (year)		61.1±6.6		61.1±7.1	0.978
Sex					0.439
Male	22		26		
Female	32		28		
Body mass index (kg/m²)		23.23±2.01		23.13±1.98	0.997
Disease duration (year)		3.94±1.51		4.27±1.55	0.773
Location of injury					0.441
Left	24		25		
Right	30		29		

SD: Standard deviation.

TABLE 3
Comparison of various indexes between the two groups

	Control group			Research group			
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment		
	Mean±SD	Mean±SD	p^1	Mean±SD	Mean±SD	p^2	p^3
Michel Lequesne (score)	8.54±1.62	4.00±1.44	<0.001	8.46±1.42	3.15±1.37	<0.001	0.002
VAS (score)	4.11±1.19	2.93±1.08	<0.001	4.39±1.09	1.33±1.03	<0.001	<0.001
LKSS (score)	49.98±5.55	72.91±7.40	<0.001	50.83±5.55	86.72±8.59	<0.001	<0.001
ESR (mm/h)	21.91±10.22	11.18±2.55	<0.001	21.66±10.30	9.72±3.59	<0.001	0.017
CRP (mg/L)	8.26±3.01	2.07±0.30	<0.001	8.20±3.15	1.90±1.01	<0.001	<0.001
IL-1β (ng/mL)	87.26±10.59	64.91±9.24	<0.001	85.18±10.02	45.40±6.74	<0.001	<0.001
IL-6 (pg/mL)	233.75±38.53	163.67±20.91	<0.001	225.68±43.14	102.29±16.14	<0.001	<0.001
TGF-β (μg/L)	19.07±9.20	26.27±7.00	<0.001	19.59±9.92	31.04±5.46	<0.001	<0.001
IGF-1 (μg/L)	79.94±9.67	89.87±7.40	<0.001	79.89±11.08	95.16±8.12	<0.001	0.001
FGF-2 (μg/L)	21.70±2.84	26.42±4.57	<0.001	22.88±2.93	31.85±3.41	<0.001	<0.001
p38 MAPK	1.02±0.22	1.00±0.19	<0.001	0.82±0.20	0.32±0.03	<0.001	<0.001

SD: Standard deviation; VAS: Visual Analog Scale; LKSS: Lysholm Knee Scoring Scale; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; IL-1β: Interleukin-1beta; IL-6: Interleukin-6; TGF-β: Transforming growth factor-beta; IGF-1: Insulin-like growth factor-1; FGF-2: Fibroblast growth factor-2; p^1 represents the intra group comparison of the control group; p^2 represents the intra group comparison of the research group; p^3 represents an intergroup comparison between the research group and the control group after treatment.

TABLE 4
Comparison of clinical efficacy between the two groups

	Control group (n=54)		Research group (n=54)		
Satisficing	n	%	n	%	*p*
Clinical control	7	12.96	12	22.22	
Markedly effective	25	46.30	27	50.00	
Effective	7	12.96	10	18.52	<0.001
Ineffective	15	27.78	5	9.26	
Total effective rate	39	72.22	49	90.74	

TABLE 5
Correlation analysis between p38 MAPK and various indicators

	Pre-treatment		Post-treatment	
Characteristics	r	*p*	r	*p*
Michel Lequesne (score)	0.493	<0.001	0.477	<0.001
LKSS (score)	-0.381	0.005	-0.309	0.023
VAS (score)	0.318	0.019	0.274	0.045
ESR (mm/h)	0.401	0.003	0.516	<0.001
CRP (mg/L)	0.683	<0.001	0.644	<0.001
IL-1β (ng/mL)	0.515	<0.001	0.541	<0.001
IL-6 (pg/mL)	0.726	<0.001	0.741	<0.001
TGF-β (μg/L)	-0.532	<0.001	-0.378	0.005
IGF-1 (μg/L)	-0.307	0.024	-0.307	0.024
FGF-2 (μg/L)	-0.417	0.002	-0.326	0.016

VAS, Visual Analog Scale; LKSS, Lysholm Knee Scoring Scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-1β, interleukin-1beta; IL-6, interleukin-6; TGF-β, TGF-beta1; IGF-1, insulin-like growth factor-1; FGF-2, fibroblast growth factor-2.

scores showed no significant difference between the two groups before treatment. The VAS scores in both groups were significantly lower than after treatment, and the scores in the research group were lower than those in the control group ($p<0.001$). After treatment, LKSS scores in both groups were significantly higher than before treatment. Notably, the LKSS scores after treatment were higher in the research group than in the control group ($p<0.001$). The results of inflammatory indicators showed that ESR, CRP, IL-1β, and IL-6 were significantly down-regulated in both groups after treatment compared to those before treatment. After treatment, the levels of these indicators in the research group were lower than those in the control group ($p<0.05$). Moreover, the results of growth factor assessment showed that the serum levels of TGF-β, IGF-1, and FGF-2 were significantly upregulated after treatment than before treatment, and the growth factors were higher in the research group than in the control group after treatment ($p<0.001$). Additionally, qRT-PCR showed that the level of p38 MAPK mRNA in the blood of both groups decreased significantly after treatment. It was also observed that the reduction of p38 MAPK was greater in the research group after treatment than in the control group ($p<0.001$).

Comparison of clinical efficacy

The evaluation of clinical efficacy is summarized in Table 4. The overall effective rate of the research group was 90.74%, which was significantly higher than that of the control group (72.22%; $p<0.001$), indicating that the efficacy of the study group was better than that of the control group.

Correlation analysis between p38 MAPK and each indicator

The Pearson correlation analysis results of p38 MAPK level and each index in the research group before and after treatment are shown in Table 5. The results showed that the levels of the ISOA score, VAS score, LKSS score, ESR, CRP, IL-1β, IL-6, TGF-β, IGF-1, and FGF-2 in the research group were correlated with the levels of p38 MAPK before and after treatment. Among these parameters, LKSS score, TGF-β, IGF-1, and FGF-2 were significantly negatively correlated with p38 MAPK, while the ISOA score, VAS score, ESR, CRP, IL-1β, and IL-6 were significantly positively correlated with p38 MAPK. Among these markers, the inflammatory markers ESR, CRP, IL-1β, and IL-6 showed a strong correlation with p38 MAPK.

DISCUSSION

Acupuncture, as one of the important treatment methods of traditional Chinese medicine, has a certain curative effect on the treatment of KOA.[23] Acupoints selected for the treatment of KOA are mainly those around the knee joint, which is determined according to the anatomical structure of the knee joint.[24] In this study, we selected four acupoints, namely the inner knee eye (EX-LE4), outer knee eye (EX-LE5), Yanglingquan (GB34), and Zusanli (ST36). The function of the above-mentioned acupoints is to promote blood circulation, and they are often used to treat leg pain, joint pain, peripheral soft tissue inflammation, and other skeletal muscle diseases caused by various reasons.

In this study, there was no significant difference in baseline data between the two groups of patients, indicating that the two groups of patients have the research value of a comparative study. The results of this study showed that the overall curative effect of acupuncture combined with basic treatment on KOA was significantly higher than that of sham acupuncture combined with basic treatment (90.74% *vs.* 72.22%). After four weeks of treatment, acupuncture combined with basic treatment can significantly reduce the Michel Lequesne score and VAS scores, as well as improve LKSS scores. In addition, compared to the sham acupuncture combined with basic treatment, the levels of ESR, CRP, IL-1β, and IL-6 in the acupuncture group were significantly reduced after treatment, while the levels of TGF-β, IGF-1, and FGF-2 were significantly increased. Meanwhile, through the detection of MAPK signaling pathway, it was found that acupuncture combined with basic treatment could significantly reduce the relative expression of p38 MAPK mRNA. The results suggested that acupuncture combined with basic treatment has achieved significant positive effects on the improvement of knee pain and function.

The occurrence and development of KOA is closely related to the inflammatory response. Acute KOA is mainly characterized by joint swelling, pain, and functional limitation, which is related to the accumulation of oxidative stress products and the activation of inflammation induced by meniscus and synovial injury during KOA.[25] Synovial inflammation can induce a cascade reaction through the release of inflammatory factors such as IL-1β and TNF-α, promote the progression of synovial inflammation, and further aggravate the injury of KOA. Shi et al.[26] found that acupuncture can significantly reduce

the levels of proinflammatory cytokines (TNF-α and IL-1β) and cartilage degradation biomarkers (MMP (matrix metalloproteinase)-3 and MMP-13), as well as significantly increase the levels of the anti-inflammatory cytokine IL-13. In this study, inflammation indexes in both groups were significantly lower after treatment than before, indicating that inflammation in patients with KOA was suppressed after treatment. However, it can be observed that the inflammation index of acupuncture combined with the basic treatment group is lower than that of sham acupuncture combined with the basic treatment group.

Interleukin-1β is one of the strongest inflammatory cytokines in the body, and its content is very low under physiological conditions. However, it is greatly increased when diseases such as gout and arthritis occur, which can directly participate in cartilage degradation, accelerate synovial hyperplasia, and induce chondrocyte growth arrest.[27] Cartilage injury is a key feature of KOA. In current clinical practice, there is still a lack of effective treatment to reverse cartilage injury, and it can only delay the injury process as much as possible. Tissue growth factor-β is an important factor in chondrogenesis and cartilage damage repair, and the continuous reduction of its level is not conducive to the recovery of KOA.[28] Similarly, IGF-1 and FGF-2 are growth-promoting endocrine hormones that can protect cartilage and delay cartilage degeneration in joints, but if they are insufficiently expressed in the serum of KOA patients, they may be unfavorable to disease control.[29,30] It could be gathered that acupuncture combined with basic treatment in this study can alleviate the clinical symptoms of patients and reduce the inflammatory reaction of joints, thus promoting the recovery of joints.

In recent years, the pathogenesis and targeted therapy of KOA have gradually become a focus of research, mainly focusing on proteomics, gene expression, signaling pathway, and other aspects, among which the signaling pathway is closely related to the occurrence and development of KOA. It was found that the nuclear factor-kappa B pathway, Wnt pathway, Notch pathway, and MAPK pathways were involved in the regulation of KOA.[31] Mitogen-activated protein kinases are a group of serine-threonine protein kinases that can be activated by cytokines, growth factors, and neurotransmitters.[32] As one of the important intracellular signal transduction systems, MAPKs are responsible for regulating and maintaining inflammatory response, cell growth and differentiation, and the body's adaptation to environmental stress.[33] The p38 MAPK signaling pathway is a crucial part of the MAPK family. Both inflammatory factors and stress responses can promote the phosphorylation of p38 MAPK, thus activating p38 MAPK to participate in the occurrence and regulation of inflammatory pain.[34] In the current study, through the detection of p38 MAPK mRNA in the blood of patients, it was observed that the expression of p38 MAPK mRNA in patients was decreased after treatment, which was more significantly reduced in the research group than in the control group during the same period. These results suggest that acupuncture stimulation at acupoints may have a certain inhibitory effect on local tissue inflammation and reduce the production of inflammatory factors, thus reducing the phosphorylation level of p38 MAPK. Pearson correlation study showed that the level of p38 MAPK in the research group was correlated with ISOA score, VAS score, LKSS score, ESR, CRP, IL-1β, IL-6, TGF-β, IGF-1, and FGF-2 levels to varying degrees before and after treatment. Interleukin-1β and IL-6 showed significant positive correlation with p38 MAPK levels. This result may be explained by the involvement of the p38 MAPK signaling pathway in inflammation regulation. As Zheng et al.[35] reported in a study on lung injury, serum IL-1β expression was reduced in acute lung injury rats with the inhibition of the p38 MAPK signaling pathway. Another study has shown that p38 MAPK can promote the expression of a variety of proinflammatory factors, and inflammatory factors can in turn activate the p38 MAPK signaling pathway, making the inflammatory response gradually stronger through the positive feedback pathway.[36] Therefore, based on the current results, we can only judge that p38 MAPK is involved in inflammation regulation and is associated with IL-1β and IL-6, but the regulatory mechanisms of p38 MAPK, IL-1β, and IL-6 need to be further studied.

This study has some limitations. *(i)* This study is a single-center study with a small sample size, and selection bias may inevitably occur in the process of sample inclusion. Therefore, the results of this study need to be verified in a large multi-center sample. *(ii)* Current studies suggest that the p38 MAPK signaling pathway may be involved in the regulation of inflammation in KOA, but the specific regulatory mechanisms are unknown because animal studies have not been conducted. *(iii)* This study only evaluated the short-term efficacy, but did not evaluate the long-term efficacy and safety, which needs to

be further improved to provide a new basis for the acupuncture treatment of KOA.

In conclusion, this study showed that based on the basic treatment, acupuncture had a significant effect on the treatment of KOA, which might be achieved by inhibiting the related proteins of p38 MAPK signaling pathway, thereby reducing inflammatory response and promoting cartilage repair. This is of great value in alleviating the clinical symptoms of KOA and controlling the progression of the disease. This study provides important clinical data supporting the feasibility of acupuncture in the clinical therapy of KOA.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Designed the research study, analyzed the data and wrote the manuscript: Y.W.; Performed the research: Y.W., L.Y.L., H.Q.G.; All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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