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Electroacupuncture combined with extracorporeal shock wave therapy improves pain symptoms and inflammatory factor levels in knee osteoarthritis patients

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ABSTRACT

Objective: To compare the clinical efficacy and safety of electroacupuncture combined with extracorporeal shock wave therapy (EESWT) and extracorporeal shock wave therapy (ESWT) in the treatment of knee osteoarthritis (KOA).
Methods: A total of 135 KOA patients who received EESWT treatment were selected as the EESWT group, and 135 KOA patients who received extracorporeal shock wave therapy (ESWT) were selected as the ESWT group. The clinical efficacy, inflammatory factors in joint synovial fluid and adverse events during treatment were compared before and after treatment.
Results: The clinical effective rate of patients in the EESWT group (89.63 %) after treatment was significantly higher than that of the ESWT group (74.81 %) ($p < 0.01$). The lysholm kness (LKSS) score and range of motion (ROM) of the patients in the EESWT group after treatment were higher than those of the ESWT group, while Lequesne index score, visual analogue scale (VAS) score and Western Ontario and McMaster Universities Arthritis Index (WOMAC) were lower than those of the ESWT group ($p < 0.01$). Compared with ESWT group, the changes in the expression levels of nitric oxide (NO), superoxide dismutase (SOD), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), matrix metalloproteinase-3 (MMP-3), and transforming growth factor β1 (TGF-β1) in the synovial fluid of the EESWT group after treatment were significantly greater than those of the ESWT group ($p < 0.01$). No significant difference in the incidence of adverse events between the EESWT group and the ESWT group ($p > 0.05$).
Conclusion: EESWT significantly improves pain symptoms and inflammatory factor levels in KOA patients and is an optional KOA treatment option worthy of clinical attention.

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1. Introduction

KOA is a kind of joint degenerative disease that occurs in middle-aged and elderly people. Its pathological features are mainly degeneration and destruction of articular cartilage, subchondral bone sclerosis, synovial hyperplasia, osteophyte formation, soft tissue contractures, etc. KOA can cause knee joint pain, dysfunction, deformity and other symptoms, with high morbidity and disability, which seriously affects the KOA patients' life quality [1,2].

At present, the clinical treatment of advanced KOA often uses artificial knee replacement, while for early and mid-term KOA patients, medications, physical therapy, functional exercises and other treatment methods are used to reduce symptoms or delay the development of the disease [1,3,4]. Researchers have found that electroacupuncture can reduce cartilage degeneration by relieving pain and enhancing muscle function in a knee osteoarthritis model [5]. ESWT is originally used to treat urinary calculi, and then gradually expands to the treatment of musculoskeletal diseases [6,7]. High-energy ESWT is often used to treat nonunion, avascular necrosis of the femoral head and other diseases [8], while low-energy ESWT is mostly used to improve the symptoms of soft tissue pain diseases such as plantar fasciitis [9] and lateral epicondylitis [10].

A number of studies have confirmed that electroacupuncture can effectively control the progression of KOA by inhibiting the expression of IL-1β, TNF-α, MMP-3, tissue inhibitor of metalloproteinases (TIMP)-1, TGF-β1 in articular cartilage and synovial tissue and free radical metabolism in serum, thereby reducing the inflammatory reaction around the joints, improving microcirculation, relieving muscle spasms, having a positive effect on joint mobility, and exerting an analgesic effect on the joints [11–15].

However, the pathogenesis of KOA is more complicated, and a single treatment method has certain limitations. In this study, we used EESWT to treat KOA patients, and analyzed the effect of EESWT on the pain symptoms and inflammatory factor expression levels of KOA patients, and horizontally compared the efficacy and safety of electroacupuncture combined with extracorporeal shock wave therapy, further enriching the treatment options for KOA.

2. Materials and methods

2.1. Subjects

From August 2018 to October 2020, we screened 155 KOA patients, and 20 patients were excluded. Among them, 14 did not meet the inclusion criteria, 3 did not sign informed consent, and 3 patients did not complete the treatment or lost contact. Inclusion criteria: (1) the diagnostic criteria of KOA conform to American College of Rheumatology (ACR) [16,17]; (2) Kellgren-Lawrence (K-L) [18] staging is stage I, stage II or stage III; (3) The heart, lung, liver, and kidney functions are good, and they can tolerate ESWT; (4) no drugs or knee arthroscopic surgery has been used for treatment in the past 3 months; (5) the informed consent form was signed; (6) Chinese Han population. Exclusion criteria: (1) KL staging is stage 0 and stage IV; (2) rheumatoid arthritis, rheumatoid arthritis, traumatic arthritis, gouty arthritis; (3) there is a wound on the affected knee or tuberculosis, infection, osteomyelitis in the affected limb; (4) suffering from vascular and neurological diseases; (5) the affected knee has severe varus deformity; (6) combining severe primary diseases such as liver, kidney, cardiovascular and cerebrovascular and hematopoietic systems diseases; (7) with severe osteoporosis; (8) breast-feeding or pregnant women; (9) those who cannot tolerate ESWT due to pain and other factors; (10) the content of knee joint fluid is too small to meet the testing needs; (11) have a disease that affects the level of inflammatory factors. The flow of this assay was shown in Fig. 1. This study was approved by the ethics committee of Shanghai Tenth people's hospital.

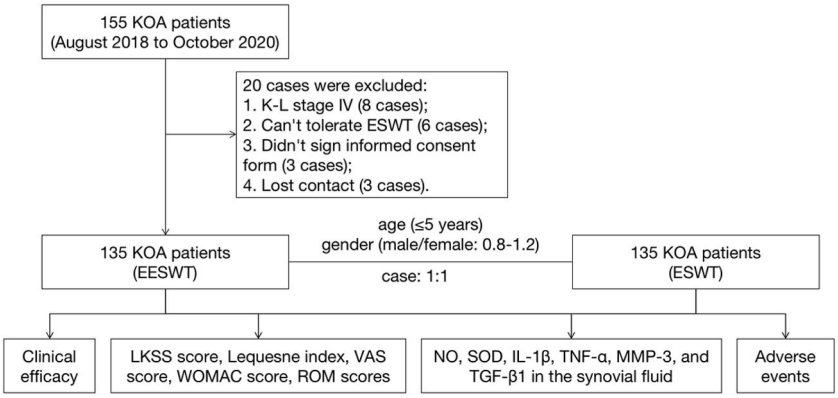

Fig. 1. The flow of the assay. KOA: knee osteoarthritis. ESWT: extracorporeal shock wave therapy. EESWT: electroacupuncture combined with extracorporeal shock wave therapy. LKSS: lysholm kness. VAS: visual analogue scale. WOMAC: Western Ontario and McMaster Universities Arthritis Index. ROM: range of motion. NO: nitric oxide. SOD: superoxide dismutase. IL-1β: Interleukin-1β. TNF-α: tumor necrosis factor α. MMP-3: matrix metalloproteinase-3. TGF-β1: transforming growth factor-β1.

2.2. Therapeutic intervention

The implementation of electroacupuncture interventions was carried out by 2 acupuncturists with 3 years or more of clinical operation experience. Before the trial, two acupuncturists were trained on the plan, and the training results met the requirements. The electroacupuncture treatment is 2 weeks a course, 10 times and 30 min each time. The specific operation is as follows: the patients were in the supine position, and then the local skin of the affected knee was disinfected. Disposable acupuncture needles (0.30mm × 75 mm) were used to pierce the Neixiyan (EX-LE 5) and Dubi (ST 35) about 50 mm. Another single-use acupuncture needle (0.30mm × 40 mm) was used to directly prick the Xuehai (SP 10) and Liangqiu (ST 34) about 30 mm according to the traditional Chinese medicine meridian theory [19,20]. After the needle was inserted, the needle produced a feeling of soreness, numbness, swelling, pain and so on. Then connected to the G6805-II electroacupuncture instrument (Shanghai Medical Electronic Instrument, China), with a pair of electrodes connecting to Liangqiu and Dubi, and another pair connecting to Xuehai and the Neixiyan. The wave type was continuous wave with a frequency of 10 Hz, and the intensity of the electroacupuncture was slowly adjusted to the patient's knee joint obviously feels soreness and swelling could be tolerated. Kept the needle for 30 min.

ESWT: Taken the local pain point around the affected knee joint as the impact point, the extracorporeal shock wave machine (MASTERPULS MP100, STORZ, Switzerland) was used to focus the shock wave energy on the impact point, the impact frequency is 10 Hz, and the treatment energy is 3 bars [21]. The optimal dose was when the patient felt that they could tolerate painful stimulation, with 2000 shocks per site, once per week, 5 times in total.

2.3. Evaluation indicators

The criteria for clinical efficacy include joint pain, joint swelling, joint mobility and walking function. (1) Joint pain:0 points for no change in joint pain, 1 point for relief, 2 points for obvious relief, and 3 points for pain disappearance. (2) Joint swelling: 0 points for no change, 1 point for relief, and 2 points for remission. (3) Joint activity: 0 points for no change, 1 point for improvement, 2 points for return to normal. (4) Walking function: 0 points for no change, 1 point for improvement, 2 points for obvious improvement, 3 points for return to normal. The clinical efficacy is judged based on the sum of the scores of the above 4 items. A score of 0–1 indicates invalid, a score of 2–5 indicates effective, a score of 6–8 indicates significant effect, and a score of 9–10 indicates clinical recovery.

The LKSS score [22] was performed before and after treatment. The LKSS score includes 8 symptoms and signs, mainly two aspects of the patient's daily exercise function and knee symptoms. The total score is 0–100 points. The higher the score, the better the functional state of the patient's knee joint.

Lequesne index score [23]: The Lequesne index score contains 3 indexes, namely pain or discomfort, maximum distance walked, daily activity, which are evaluated once before and after treatment, and each score ranges from 0 to 8 points. The heavier the pain, the more difficult it is to walk, the more restricted the ability to move, and the higher the score. The total score is 0–24 points.

VAS scores were also performed before and after treatment [24,25]. Using a 100 mm long score card with numbers, from "painless" (0 point) to "most severe pain" (100 points), patients draw a cross line where they best reflect their pain level.

The WOMAC scale includes 3 items of pain, stiffness and joint function, a total of 24 items, with a total score of 96 points. The higher the score, the worse the knee joint function [26].

ROM was assessed once before and after treatment [27]. Use wireless portable muscle strength test and joint activity meter (MicroFET3) for mobility measurement. Instruct the subject to lie on the prone position and straighten the lower limbs. The tester fixes the subject's thigh with one hand, and fixes the device with the other hand to the subject's lower leg close to the ankle joint, so that the patient bends the knee joint and reads the ROM.

A portable muscle strength test and a joint range meter (MicroFET3) are used for range of motion measurement. The test subject took the prone position and straightened the lower limbs. The tester fixed the subject's thigh with one hand, and the other hand fixed the device on the outside of the subject's calf close to the ankle joint, the ROM was read after the patient flexed the knee joint.

2.4. Laboratory testing indicators

Collected the joint fluid of the patient before and after treatment, and the nitrate reductase method was used to detect the expression level of NO [28]. Enzyme-linked immunosorbent assay (ELISA) was used to detect IL-1β (#ab214025, Abcam, Cambridge, UK), TNF-α (#ab181421, Abcam, Cambridge, UK), TGF-β1 (#ab100647) and MMP-3 (#ab269371, Abcam, Cambridge, UK) expression level. Xanthine oxidase method was used to detect SOD level [29].

2.5. Statistical analysis

In this study, the data of continuous variables such as Age, BMI, LKSS, VAS, Lequesne index score, WOMAC and ROM were presented in the form of mean ± standard deviation (mean ± SD), and differences between groups were analyzed by *t*-test. Categorical variables were expressed by frequency [n (%)], and Chi-square test was used for statistical analysis between groups, and $p < 0.05$ indicated that the difference was statistically significant. In this study, statistical analysis was performed using SPSS 26.0 software package (IBM Corp., SPSS Statistics for Mac, Version 26.0. Armonk, NY). The sample size was calculated using the comparison method of two independent sample rates [30].

3. Results

3.1. Clinical data

The clinical data of KOA patients in the EESWT group and the ESWT group were shown in Table 1. A total of 52.59 % males in the EESWT group, aged 35–87 years old, with an average of (57.96 ± 10.48) years old. In the ESWT group, males accounted for 49.63 %, aged 35–85 years old, with an average of (58.16 ± 7.67) years old. The results of statistical analysis showed that there was no statistical difference between the EESWT group and the ESWT group in terms of age, gender, body mass index (BMI), lysholm kness score, Lequesne index, VAS score, WOMAC, range of motion (ROM), and Kellgren-Lawrence (KL) stage before treatment ($p > 0.05$).

3.2. Clinical efficacy

After treatment, 20 patients in the EESWT group recovered, 66 patients had significant effects, 35 patients had clinical effects, and 14 patients with no obvious curative effect. In the ESWT group, 8 patients recovered after treatment, 34 patients had obvious clinical effects, 59 patients had clinical effects, and 34 patients had no obvious effects. The analysis results showed that the clinical effective rate of patients in the EESWT group (89.63 %) after treatment was significantly higher than that of the control group (74.81 %), and the difference was statistically significant ($p < 0.01$) (Table 2).

3.3. LKSS score

The total score of LKSS and the score of each factor before and after treatment were shown in Table 3. After treatment, the LKSS total score and limp, using cane or crutches, locking sensation in the knee, giving way sensation from the knee, pain, swelling, climbing stairs, and squatting of the KOA patients in ESWT group and EESWT group were significantly increased ($p < 0.05$), and the LKSS total score and limp, using cane or crutches, locking sensation in the knee, giving way sensation from the knee, pain, swelling, climbing stairs, and squatting of the EESWT group were significantly higher than ESWT group, the differences were statistically significant ($p < 0.05$).

3.4. Lequesne index score

The Lequesne index of the two groups of patients before and after treatment was shown in Table 4. Before treatment, there were no statistically significant differences in total score, pain or discomfort, maximum distance walked and daily activity between the two groups of patients ($p > 0.05$). After treatment, the total scores of Lequesne index and pain or discomfort, maximum distance walked and daily activity of patients in ESWT and EESWT groups were significantly reduced ($p < 0.05$), the total scores of Lequesne index, pain or discomfort, maximum distance walked and daily activity of KOA patients treated with EESWT decreased more significantly ($p < 0.05$). These results showed that compared with ESWT treatment, EESWT treatment had more advantages in reducing the severity of KOA.

3.5. VAS, WOMAC and ROM scores

The results of VAS, WOMAC and ROM scores before and after treatment were shown in Table 5. The ROM of KOA patients were significantly increased after treatment ($p < 0.01$), while both VAS score and WOMAC were significantly reduced ($p < 0.01$). Moreover,

Table 1
General information of the EESWT group and the ESWT group.

	EESWT(n = 135)	ESWT(n = 135)	*p*-value
Age(years, mean ± SD)	57.96 ± 10.48	58.16 ± 7.67	0.86
Gender[n(%)]			0.63
male	71(52.59 %)	67(49.63 %)	
female	64(47.41 %)	68(50.37 %)	
Body mass index (kg/m^2, mean ± SD)	22.85 ± 2.72	23.05 ± 3.07	0.57
LKSS(score, mean ± SD)	46.50 ± 7.05	46.48 ± 8.82	0.98
Lequesne index (score, mean ± SD)	16.61 ± 1.30	16.59 ± 1.57	0.89
VAS(score, mean ± SD)	6.54 ± 1.36	6.52 ± 1.33	0.90
WOMAC (score, mean ± SD)	47.04 ± 7.78	47.91 ± 7.91	0.36
ROM(°, mean ± SD)	90.16 ± 4.39	89.07 ± 6.45	0.11
K-L grade[n(%)]			0.61
I	35(25.93 %)	29(21.48 %)	
II	73(54.07 %)	74(54.81 %)	
III	27(20.00 %)	32(23.70 %)	

SD, standard deviation. LKSS, Lysholm Kness. ROM, range of motion. K-L, Kellgren-Lawrence. VAS, visual analogue scale. WOMAC, Western Ontario and McMaster Universities Arthritis Index. EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy.

Table 2
Comparison of clinical efficacy between the EESWT group and the ESWT group.

	Clinical recovery	Significant effect	Effective	Invalid	Effectiveness
EESWT (n = 135)	20 (14.81 %)	66 (48.89 %)	35 (25.93 %)	14 (10.37 %)	89.63 %
ESWT (n = 135)	8(5.93 %)	34 (25.19 %)	59 (43.70 %)	34 (25.19 %)	74.81 %
p-value					<0.01

EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy.

Table 3
Comparison of LKSS scores between ESWT group and EESWT group before and after treatment.

	ESWT (n = 135)		EESWT (n = 135)	
	before treatment	after treatment	before treatment	after treatment
Total score	48.07 ± 8.41	59.38 ± 8.40[a]	47.49 ± 8.77	69.18 ± 8.77[ab]
Limp	4.09 ± 1.34	4.26 ± 1.27[a]	4.01 ± 1.21	4.64 ± 0.77[ab]
Using cane or crutches	4.26 ± 1.27	4.00 ± 1.64[a]	4.03 ± 1.51	4.56 ± 1.07[ab]
Locking sensation in the knee	10.88 ± 4.04	11.96 ± 3.75[a]	10.56 ± 3.97	13.46 ± 2.82[ab]
Giving way sensation from the knee	11.56 ± 4.03	12.85 ± 3.48[a]	11.37 ± 4.25	14.48 ± 4.62[ab]
Pain	5.41 ± 2.87	9.78 ± 3.90[a]	5.37 ± 2.49	12.52 ± 4.36[ab]
Swelling	5.41 ± 2.33	6.48 ± 2.04[a]	5.43 ± 1.50	7.70 ± 2.15[ab]
Climbing stairs	4.53 ± 2.48	6.24 ± 3.16[a]	4.56 ± 2.39	7.69 ± 2.56[ab]
Squatting	2.19 ± 1.11	3.50 ± 1.15[a]	2.16 ± 1.59	4.13 ± 0.81[ab]

EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy. [a]$p < 0.05$, compared with before treatment. [b]$p < 0.05$, compared with ESWT group.

Table 4
Comparison of Lequesne index between ESWT group and EESWT group before and after treatment.

	ESWT (n = 135)		EESWT (n = 135)	
	before treatment	after treatment	before treatment	after treatment
Total score	16.59 ± 1.57	11.16 ± 2.09[a]	16.61 ± 1.30	9.85 ± 1.84[ab]
Pain or discomfort	5.34 ± 0.94	3.92 ± 1.13[a]	5.32 ± 0.84	3.37 ± 0.97[ab]
Maximum distance walked	5.81 ± 0.87	3.81 ± 1.19[a]	5.84 ± 0.83	3.49 ± 1.20[ab]
Daily activity	5.43 ± 1.10	3.43 ± 1.16[a]	5.45 ± 0.89	2.99 ± 1.13[ab]

EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy. [a]$p < 0.05$, compared with before treatment. [b]$p < 0.05$, compared with ESWT group.

Table 5
Comparison of VAS, WOMAC and ROM scores between the EESWT group and the ESWT group.

Group	VAS		WOMAC		ROM	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
EESWT(n = 135)	6.54 ± 1.36	2.34 ± 1.30[ab]	47.04 ± 7.78	24.79 ± 3.08[ab]	90.16 ± 4.39	126.39 ± 15.59[ab]
ESWT(n = 135)	6.52 ± 1.33	4.14 ± 1.37[a]	47.91 ± 7.91	33.72 ± 7.55[a]	89.07 ± 6.45	102.12 ± 14.68[a]

VAS, visual analogue scale. WOMAC, Western Ontario and McMaster Universities Arthritis Index. ROM, range of motion. EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy. [a]$p < 0.05$, compared with before treatment. [b]$p < 0.05$, compared with ESWT group.

the ROM of the patients in the EESWT group after treatment were higher than those of the ESWT group, while VAS score and WOMAC were lower than those of the ESWT group, and the difference were statistically significant ($p < 0.01$). This showed that EESWT significantly improved the pain symptoms and joint function of KOA patients than using ESWT alone.

3.6. Inflammatory indicators in synovial fluid

The expression levels of NO, SOD, IL-1β, TNF-α, MMP-3, and TGF-β1 in the synovial fluid before and after treatment were shown in Fig. 2. After treatment, the levels of NO (Fig. 2a), IL-1β(Fig. 2c), TNF-α (Fig. 2d), and MMP-3 (Fig. 2e) in the joint synovial fluid of the two groups were significantly reduced, while the levels of SOD (Fig. 2b), and TGF-β1 (Fig. 2f) were significantly increased ($p < 0.01$). Compared with before treatment, the changes in the expression levels of NO, SOD, IL-1β, TNF-α, MMP-3, and TGF-β1 in the synovial fluid of the EESWT group after treatment were significantly greater than those of the ESWT group, and the differences were statistically significant ($p < 0.01$).

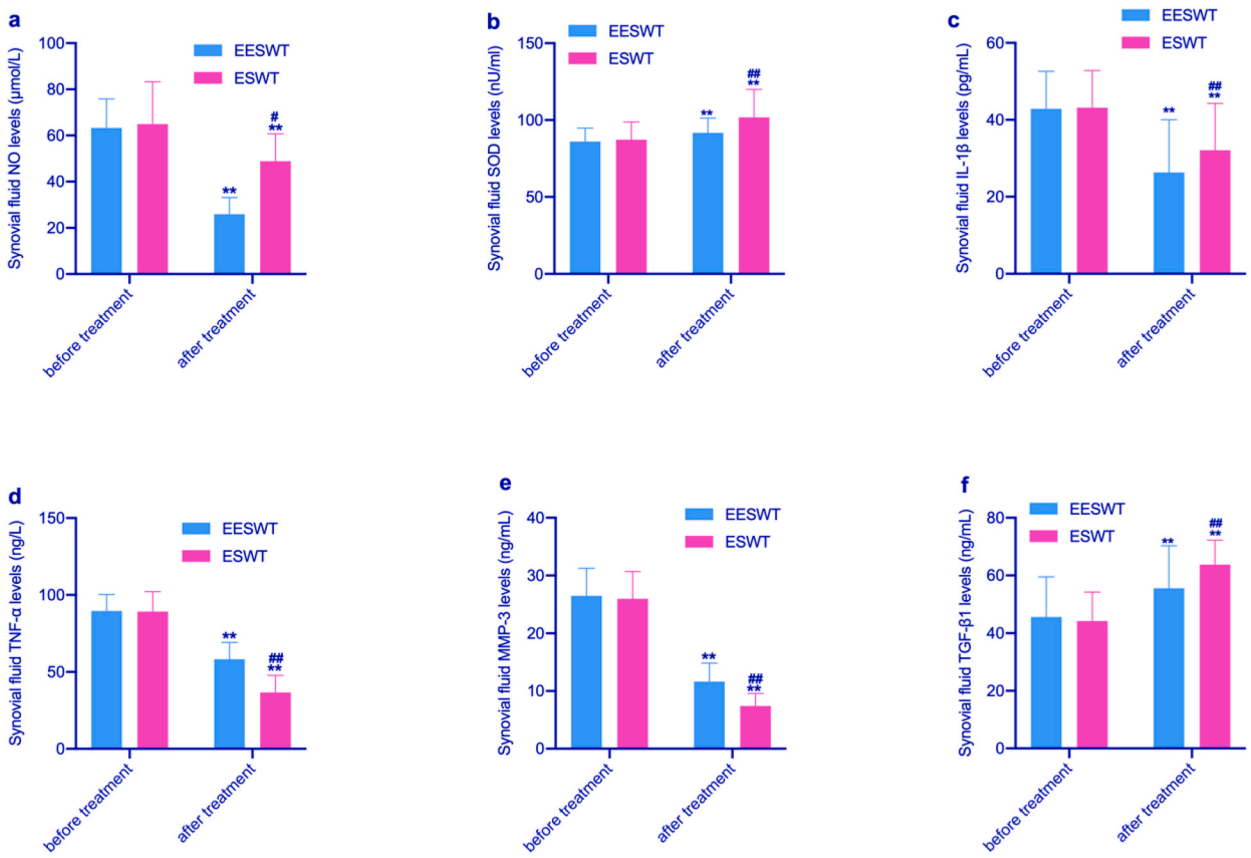

Fig. 2. Changes in the expression levels of NO, SOD, IL-1β, TNF-α, MMP-3 and TGF-β1 in synovial fluid before and after treatment. a–f: NO, SOD, IL-1β, TNF-α, MMP-3 and TGF-β1, respectively. $^{**}p < 0.01$, compared with before treatment. $^{\#\#}p < 0.01$, compared with Control group. EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy. NO: nitric oxide. SOD: superoxide dismutase. IL-1β: Interleukin-1β. TNF-α: tumor necrosis factor α. MMP-3: matrix metalloproteinase-3. TGF-β1: transforming growth factor-β1.

3.7. Adverse reactions

Adverse events during treatment mainly include joint swelling, joint puffiness, joint pain and joint stiffness (Table 6). The results of the analysis showed that there was no significant difference in the incidence of adverse events during treatment between the EESWT group and the ESWT group ($p > 0.05$).

4. Discussion

We know that the occurrence of KOA is related to a variety of cytokines, the cytokine content in knee joint fluid is related to the severity and progression of KOA [31]. Cytokines related to the occurrence of KOA are divided into decomposing factors and synthetic factors. The decomposing factors are mostly NO, IL-1β, TNF-α, MMP-3, etc. [32–35]. IL-1β is an inflammatory factor that is widely present in tissue cells and has a powerful inflammatory effect. IL-1β up-regulated Wnt-5A protein by activating the JNK pathway, induced the expression of *MMP-3* gene, promoted the degradation of articular cartilage matrix and inhibited the expression of type II collagen, reduced the key components of the synthesis of extracellular cartilage matrix such as type II collagen and aggrecan [36]. It is the most critical initiating factor that promoted the destruction of KOA articular cartilage and cartilage matrix degradation, and played

Table 6
Comparison of adverse events between the study group and the control group.

	EESWT (n = 135)	ESWT (n = 135)	*p* value
Joint swelling	5(3.70 %)	8(5.93 %)	0.39
Joint puffiness	9(6.67 %)	7(5.19 %)	0.61
Joint pain	7(5.19 %)	10(7.41 %)	0.45
Joint stiffness	4(2.96 %)	3(2.22 %)	0.70

EESWT, electroacupuncture combined with extracorporeal shock wave therapy. ESWT, extracorporeal shock wave therapy.

a key role in the KOA inflammation-mediated process [37,38]. In recent years, studies in cells and animal have confirmed that ESWT can stimulate cartilage repair [39,40]. Chondrocytes are sensitive to extracorporeal shock wave stress. Studies have shown that ESWT significantly promoted the proliferation of chondrocytes, inhibited the apoptosis of chondrocytes, delayed cartilage degeneration, and promoted the recovery of cartilage function [41,42].

At the same time, during the development of inflammation, IL-1β can stimulate the expression of nitric oxide synthase in cartilage and synovium, and synthesize high levels of NO, which is closely related to the development and outcome of inflammation [43]. The high level of NO in the synovial fluid caused a strong oxidative stress reaction inside and outside the cell and inhibited the proliferation of chondrocytes, induced chondrocyte apoptosis, and accelerated the progress of osteoarthritis [43]. Similar to IL-1β, TNF-α played an important role in the remodeling of KOA cartilage, which was directly proportional to the severity of KOA, and had high diagnostic value for KOA [44]. Yue et al. [45] found that reducing the levels of TNF-α and MMP-3 in articular cartilage tissue improved the motor function of KOA. As a cytokine with the ability to scavenge oxygen free radicals, SOD can prevent the destruction of cartilage cells and cell matrix of the knee joint by oxygen free radicals, and delay the process of knee osteoarthritis. Its vitality indirectly reflects the body's ability to scavenge oxygen free radicals [46,47]. Therefore, these two factors are balanced with each other to maintain the stability of the cartilage of the knee joint. When this balance is broken, the cartilage matrix of the bone and joint will be degraded and destroyed, which will eventually lead to KOA. Studies have found that ESWT down-regulated the expression of multiple inflammatory factors in knee joint chondrocytes [48–50], by inhibiting the expression of caspase-3 in chondrocytes, reducing the content of NO in synovial fluid [51], ESWT delayed the occurrence and development of OA.

In this study, compared with ESWT, the clinical efficacy of KOA patients who received EESWT was significantly improved. The expression levels of NO, IL-1β, TNF-α, and MMP-3 in joint synovial fluid were significantly reduced, which not only effectively delayed the development of OA, but also reduced the level of inflammatory factors, promoted the proliferation of cartilage cells and the repair of articular cartilage. The increased expression levels of SOD and TGF-β1 reduced the damage of inflammatory factors to the cartilage cells and cell matrix of the knee joint, delayed the development of arthritis, promoted the proliferation of chondrocytes and cartilage repair.

In addition, compared with ESWT treatment, EESWT significantly improved the KLSS score and ROM of KOA patients, and reduced Lequesne index score, VAS and WOMAC. This showed that the addition of electroacupuncture on the basis of ESWT had a significant effect and played a positive role in the pain symptoms and joint function of KOA patients. Some researchers believed that ESWT reduced the sensitivity of peripheral nerves, inhibited the expression of pain factors such as calcitonin gene-related peptide, reduced the release of substance P, inhibited pain information transmission, increased pain threshold, and have a good analgesic effect [52,53]. Some studies have also confirmed that ESWT can improve pain and function in KOA patients in the short term [54]. These studies are consistent with our findings. According to the incidence of adverse events in this study, we can see that there were few adverse reactions after electroacupuncture treatment, and the safety was good. It can be seen that ESWT not only plays an analgesic effect in the treatment of KOA, but also effectively protects cartilage, promotes cartilage remodeling, and improves the range of motion of the knee joint. It can better alleviate clinical symptoms and improve knee joint function by combining with electroacupuncture. Research have shown that electroacupuncture treatments could activate the nervous system and inhibit inflammatory and neuropathic pain by desensitizing peripheral nociceptors and reducing pro-inflammatory cytokines [11]. In recent years, people have conducted in-depth studies on ESWT and found that ESWT can reduce the sensitivity of peripheral nerves, increase the pain threshold, reduce the release of substance P and calcitonin gene-related peptide and other pain factors, inhibit the transmission of pain information, and exert a good analgesic effect.

There are some problems that need to arouse our attention when used in actual clinical work. For example, in the process of treating KOA, in order to obtain a better curative effect, the parameter setting of ESWT is one of the keys, including penetration depth, waveform, treatment pressure, energy flow density, impact frequency, number of impacts, etc., especially energy flow density plays a decisive role in the therapeutic effect of KOA. ESWT is more destructive in the high energy range, and it is prone to damage to non-treatment parts. It is mostly used for the treatment of nonunion, femoral head necrosis, urinary calculi and other diseases. However, ESWT in the middle and low energy range has relatively small damage to bone and soft tissues, and requires a short reconstruction time. Therefore, the ESWT in the middle and low energy range is mostly used for the treatment of KOA in clinic. More clinical research data is needed for the energy flux density applicable to different patients. In addition, electroacupuncture not only has a good effect in analgesia, but also can improve muscle and vasospasm, reduce local edema, and improve tissue excitability. However, the electroacupuncture effects produced by different waveforms are different. The continuous wave is used in this study, and the density wave and the discontinuous wave have not been studied yet. We have not yet studied the applicability of different waveforms, which is a problem that needs to be solved in the next research. In addition, the sample size selected in this study is small, and further study is needed in a large sample size. Another point is that we did not further analyze and compare the changes in articular cartilage in this study. I think this is one of the things that needs to be focused on in our later studies.

5. Conclusion

Through this study, we know that compared with ESWT treatment, EESWT effectively solves the limitations of a single treatment plan for KOA patients, significantly improves pain symptoms and inflammatory factor levels in KOA patients and is an optional KOA treatment option worthy of clinical attention.

Data Availability statement

Data will be made available on request.

Clinical trial and ethical standards statement

Our trial was registered retrospectively (No. ChiCTR2100051951). And our study was approved by the Ethics Committee of Ethics Committee of Shanghai Tenth People's Hospital (No. 2019-K-168).

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CRediT authorship contribution statement

Shengfu Liu: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Qiudan Chen:** Conceptualization, Data curation, Methodology, Writing – original draft. **Qinggang Zhang:** Conceptualization, Data curation, Writing – original draft. **Kun Tao:** Conceptualization, Data curation, Visualization, Writing – original draft. **Changhong Li:** Data curation, Methodology. **Baolei Chang:** Resources, Supervision, Visualization, Writing – review & editing. **Weifeng Wang:** Project administration, Validation, Writing – review & editing. **Zhong Wu:** Funding acquisition, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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