Clinical efficacy of repeated intra-articular pulsed radiofrequency for the treatment of knee joint pain and its effects on inflammatory cytokines in synovial fluid of patients

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Abstract. The application value of repeated intra-articular pulsed radiofrequency for the treatment of knee joint pain has remained to be determined. To investigate this, a total of 64 patients with chronic knee joint pain admitted to Caoxian People's Hospital (Caoxian, Chine) between October 2016 and May 2018 were enrolled in the present study and analyzed prospectively. The patients were randomly divided into a control group, receiving treatment with a single intra-articular pulsed radiofrequency through the knee joint (n=32), and an experimental group, receiving multiple intra-articular pulsed radiofrequency treatments through the knee joint (n=32). The visual analog scale score (VAS), clinical efficacy and adverse reactions prior to and after treatment were compared between the two treatments. Synovial fluid cytokines were measured using ELISA prior to and after treatment. After the treatment, the control group and the experimental group both had a lower VAS (P<0.001) and the control group had a higher VAS and lower pain relief than the experimental group (P<0.001). The control group had a total effectiveness rate of 78.13%, with 13 patients experiencing complete relief (40.63%), 12 patients exhibiting a marked improvement (37.5%) and 7 patients reporting no effects (21.87%). The experimental group had a total effectiveness rate of 90.63%, with 18 patients (56.25%) being cured, 11 patients having a marked effect (34.37%) and 3 patients reporting no effects (9.38%). The experimental group had a higher incidence of adverse reactions than the control group (P<0.05). After treatment, the two groups had decreased IL-6, IL-10 and TNF-α levels in the knee joint synovial fluid (P<0.05), with the experimental group having lower cytokine levels than the control group (P<0.05). These results indicated that repeated intra-articular pulsed radiofrequency is an effective method for the treatment of knee joint pain and may be used in clinical practice.

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Introduction

Knee joint pain, a common morbidity in clinical orthopedics, has various causes. Chronic knee pain is frequently caused by osteoarthritis (OA) (1); in elderly patients, it may be caused by rheumatoid arthritis (2). The knee joint is a complex and important joint (3) and knee joint pain severely reduces the quality of life of patients. In the clinic, treatments to alleviate pain and maintain joint mobility are selected based on the situations of individual patients. Treatment generally includes pain management, physical therapy and replacement therapy, which are usually adopted in combination. In the treatment of knee joint OA, glucosamine combined with chondroitin sulfate have relevant roles in clinical analgesia (4) and non-steroidal anti-inflammatory drugs (NSAIDs) may alleviate pain, though they are not suitable for certain patients due to their side effects, such as injury to the intestinal mucous membrane following their long-term oral use (5-7). Proximal fibula osteotomy, a novel type of surgery, may be adopted to relieve pain and improve joint function in patients, whereas partial or total knee arthroplasty should only be considered when all conservative treatment measures have been attempted (8).

Pulsed radiofrequency is widely adopted to relieve pain in clinical practice (9-11). In this process, a pulsed current emitted by a radiofrequency generator applies a high voltage to the area near the nerve tissue. Such energy transmission will neither destroy the anatomic basis of pain impulse transmission, nor destroy motor nerve function; thus, pulsed radiofrequency is a safe treatment with little risk. Erdem and Sir (12) investigated the effects of ultrasound-guided knee radiofrequency treatment on knee joint pain in patients with severe knee OA or patients who underwent knee arthroplasty and indicated that perceived pain and disability in the knee

medial nerves were relieved after the treatment. Relevant studies have confirmed that pulsed radiofrequency treatment for the knee joint, a novel technique for relieving pain in OA, is able to reduce pain, relax the muscles and improve knee function (13). Such injuries stimulate large increases in the levels of catabolic species, which contribute to progressive cartilage destruction in the synovial fluid (14). Single pulsed radiofrequency may alleviate pain, but its regulation does not last for a long period of time. To date, only a small number of clinical studies (15,16) have reported the use of repeated intra-articular pulsed radiofrequency for the treatment of knee joint pain.

Studies have indicated that knee OA is associated with inflammatory mediators (17,18). For instance, IL-6- and TNF-α-mediated diet and exercise affect the pain associated with knee OA (19). In addition, a recent study suggested that cytokine and neuropeptide levels are associated with pain and pain relief in patients with joint disease (20). Several groups have focused their attention on the potential of IL-10 as a therapeutic tool for OA therapy and prevention (21,22). IL-10 may be a useful marker for systemic inflammatory diseases (23). However, these studies may underestimate the variety of biochemical mediators implicated in long-term outcomes of OA (24). The level of inflammatory mediators may be adopted for a comprehensive diagnosis of patients with knee joint pain and provide an effective reference for successful treatment strategies, such as the main index for the degree and assessment of clinical efficacy.

The present study utilized repeated intra-articular pulsed radiofrequency to treat patients with knee joint pain and observed its clinical efficacy and safety in patients as well as its effects on IL-6, IL-10 and TNF-α levels in the synovial fluid.

Patients and methods

Subjects. A total of 64 patients with chronic knee joint pain admitted to Caoxian People's Hospital (Caoxian, China) between October 2016 and May 2018 were enrolled in our study and analyzed prospectively. The 64 patients included 31 males and 33 females between the ages of 50 and 60 years with a mean age of 52.23±11.57 years. This study was approved by the Ethics Committee of the Caoxian People's Hospital (Caoxian, China) and all subjects signed an informed consent form. Kellgren and Lawrence's radiological diagnostic criteria (25) were used, in which OA is classified into five levels: Grade 0, normal; Grade I, suspected narrowing of the joint space and possible osteophytes; Grade II, obvious osteophytes and the joint space is suspiciously narrowed; Grade III, moderate number of osteophytes, the joint space is narrowed and there are sclerosing changes; Grade IV, a large number of osteophytes, the joint space is notably narrowed and there are severe sclerosing lesions and obvious deformities.

Inclusion and exclusion criteria. The inclusion criteria were as follows: Patients between 50 and 60 years of age for whom complete clinical data were available; diagnosed with knee pain lasting for 0.5-1 years with limited joint activity; presence of a large amount of effusion confirmed by physical examination and MRI; willingness to cooperate with the medical staff at the hospital. The exclusion criteria were as follows: Patients with a history of long-term analgesic drug usage; cardio-cerebrovascular disease; severe organ failure; combined injuryperipheral neuropathy; mental disease or communication obstacles; and those transferred to another hospital half-way through the study period. Patients from whom synovial fluid collection was not successful were also excluded.

Methods. The study only included patients whose knee effusion was confirmed by physical examination and MRI. Synovial fluid was collected either directly or by small volume saline lavage when direct aspiration failed. The patients were randomly divided into a control group, who received treatment with a single intra-articular pulsed radiofrequency through the knee joint (n=32), and the experimental group, who received multiple intra-articular pulsed radiofrequency treatments through the knee joint (n=32). The subjects in the control group were treated once and those in the experimental group were treated once every two weeks (for a total of four times). The treatment period was two months.

Treatment methods. The patients were placed in a supine position on an operating table with a thin pillow under the knee. The patients were locally anesthetized by subcutaneous injection on both sides of the knee joint. Two radiofrequency trocars (10 cm long and 10 mm wide at the working end) were inserted into the knee articular cavity from the knee eyes to the center of the knee joint with assisted positioning using ultrasound-guided radiofrequency (STARmed) manipulation of the sensory nerve around the knee. A radiofrequency therapy device was connected and regulated to have a voltage of <45V and a temperature of <45˚C, for 15 min. The puncture points were covered with sterile drug film (Kanglidi aseptic dressing; China Yangzhou Guo Tai Co., Ltd.) after treatment. All operations were performed by the same group of physicians and the patients' adverse reactions were closely monitored during the treatment. If infection occurred after the operation, adequate drainage was required, bacterial culture and drug sensitivity tests were carried out on the pus and relevant antibiotics were then used for anti-infection treatment according to the drug sensitivity test.

Evaluation standards of clinical efficacy. The degree of pain in the patients was assessed by determining the visual analog scale score (VAS) prior to treatment and at a minimum of 2 years following surgery (26). The pain was scored as follows: No pain, 0; tolerable mild pain, 0-4; pain that affects sleep, 4-7; and intolerable, severe pain, 7-10.

Treatment efficacy was evaluated as follows: 'Cure' was defined as complete disappearance of knee joint disease and the patient's activity returning to normal; a 'marked effect' was defined as relieved knee joint pain and flexion and improved motion; and 'no effect' was defined as no relief or improvement in symptoms and knee function, and possibly worsening of the condition (27). The following formula was used for evaluating the efficacy of treatment: Total effective rate = (number of patients cured + number of patients with marked effect)/total number of cases.

Knee function was evaluated based on the Lysholm Knee Score Scale (LKSS) score (28) determined prior to and after treatment. Higher scores indicated better knee function.

Table I. Comparison of clinical data between the groups.

Item	Experimental group (n=32)	Control group (n=32)	χ^2 or t	P-value
Age, years	52.30±5.44	53.10±5.74	0.572	0.569
Sex			0.063	0.802
Male	15 (46.87)	16 (50.00)		
Female	17 (52.13)	16 (50.00)		
BMI, kg/m^2	24.45±2.64	23.81±2.45	1.005	0.318
Course of disease, months	1.84±1.24	1.82±1.36	0.061	0.951
Marital status		0.075	0.784	
Married	22 (68.75)	23 (71.87)		
Unmarried	10 (31.25)	9 (28.13)		
VAS			0.169	0.918
0-4	3 (9.37)	4 (12.5)		
4-7	19 (59.38)	18 (56.25)		
7-10	10 (31.25)	10 (31.25)		
Area of residence		0.063	0.802	
Town	17 (52.13)	16 (50.00)		
Rural	15 (46.87)	16 (50.00)		
Smoking			0.064	0.800
Yes	14 (43.75)	13 (40.62)		
No	18 (56.25)	19 (59.38)		
Drinking			0.063	0.801
Yes	14 (43.75)	15 (46.87)		
No	18 (56.25)	17 (52.13)		

Values are expressed as n (%) or the mean ± standard deviation. BMI, body mass index; VAS, visual analog scale score.

Detection of inflammatory cytokines. Inflammatory cytokines were determined as described previously (29). The patients' knee synovial fluid was sampled prior to and after treatment; the synovial fluid samples were centrifuged at 299 x g for 15 min at 4˚C and then stored at -80˚C. Inflammatory indexes, including IL-6 (cat. no. KIT10395; Sino Biological Inc.), IL-10 (cat. no. BE45601; IBL International) and TNF-α (cat. no. XF16189Q; Shanghai Xinfan Biotechnology Co., Ltd.) were detected through ELISA in strict accordance with the instructions of the kit. The optical density of each well was measured at a wavelength of 450 nm using a BIOBASE2000 ELISA automatic analyzer (Jinan Biobase Biotechnology Co., Ltd.). From these values, the concentrations of IL-6, IL-10 and TNF-α were then calculated.

Statistical analysis. All statistical analyses were performed using SPSS 24.0 statistical software (IBM Corp.). All graphs were generated using GraphPad 8 (GraphPad Software, Inc.). Enumeration data were expressed as n (%) and comparisons between groups were performed using the χ^2 test or Fisher's exact test. The Jarque-Bera test was used to test the normality of distribution of the data. Continuous variables were expressed as the mean ± standard deviation or median (interquartile range). Comparisons of continuous variables were assessed using the paired t-test (before vs. after treatment) or an unpaired t-test (control vs. experimental group). For ordinal variables, Mann-Whitney U tests were used for unpaired comparisons (control vs. experimental group) and Wilcoxon signed-rank tests for paired comparisons (before vs. after treatment). Bonferroni correction was applied for multiple comparisons. P<0.05 was considered to indicate a significant difference.

Results

Comparison of general characteristics and clinical parameters. No significant differences in terms of age, sex, body mass index, course of disease, marital status, VAS at baseline, area of residence, smoking, drinking and exercise status between the experimental group and the control group were present (P>0.05), which indicated that the two groups were comparable. The basic data of the two groups are presented in Table I.

VAS at different time-points. After treatment, both the control and experimental group exhibited a lower VAS and experienced pain relief (P<0.001). The control group after treatment had a higher VAS than the experimental group (4.38±1.48 and 2.48±1.25, respectively) and experienced less pain relief than the experimental group (P<0.001; Table II).

Comparison of the efficacy (%) of treatment between the groups. Treatment in the control group had a total effectiveness

Table II. Visual analog scale score of the two groups at different time-points.

Group	Before treatment	After treatment	t	P-value[a]
Control (n=32)	6 (3)	4 (5)	5.610	<0.001
Experimental group (n=32)	7 (6)	2 (3)	12.002	<0.001
P-value[b]	6 (3)	4 (5)		

[a]Wilcoxon signed-rank test; [b]Mann-Whitney U test.

Table III. Comparison of the clinical efficacy between the two groups.

Group	Cure	Marked effect	No effect	Total effective rate
Control (n=32)	13 (40.63)	12 (37.5)	7 (21.87)	25 (78.13)
Experimental group (n=32)	18 (56.25)	11 (34.37)	3 (9.38)	29 (90.63)

Values are expressed as n (%).

Table IV. Comparison of adverse reactions between the two groups.

Group	Infection	Sciatica	Deep venous embolism	Total
Experimental group (n=32)	2 (6.25)	2 (6.25)	0 (0)	4 (12.5)
Control (n=32)	1 (3.13)	0 (0)[a]	0 (0)	1 (3.13)[a]

Values are expressed as n (%). [a]P<0.05.

rate of 78.13%, with 13 patients cured (40.63%), 12 patients reporting a marked effect (37.5%) and no effect reported by 7 patients (21.87%). The experimental group had a total effectiveness rate of 90.63%, with 18 patients cured (56.25%), 11 patients reporting a marked effect (34.37%) and no effect reported by 3 patients (9.38%; Table III).

Comparison of adverse reactions (%) between the groups. In the experimental group, two patients suffered an infection (6.25%) and two patients had sciatica (6.25%). In the control group, one patient suffered an infection (3.13%). There was no evidence of deep venous thrombosis in either group. The experimental group had a higher incidence of adverse reactions than the control group (P<0.05; Table IV).

Evaluation of knee function at different time-points. After treatment, the control group and the experimental group both exhibited higher LKSS values and improved knee joint function (P<0.001). The control group after treatment had a lower LKSS value than the experimental group (73.31±9.17 and 84.24±13.52, respectively; P<0.001; Table V).

Comparison of IL-6, IL-10 and TNF-α levels. After treatment, both groups exhibited decreased concentrations of IL-6, IL-10 and TNF-α in the knee joint synovial fluid (P<0.05). The experimental group had lower concentrations of IL-6, IL-10 and TNF-α than the control group (P<0.05; and Fig. 1).

Comparison between patients with marked effects and those with no effects within the experimental group. The experimental group was divided into a marked effect group, containing 29 patients, and a no effect group, containing 3 patients, based on the clinical efficacy evaluation.

The levels of IL-6 in the marked effect group prior to and after treatment were 49.64±15.37 and 23.36±12.54 pg/ml, respectively, and those of the no effect group were 50.29±15.35 and 43.18±10.24 pg/ml, respectively. The two groups had higher IL-6 levels before treatment (P<0.05) and the marked effect group had lower IL-6 levels than the no effect group after treatment (P<0.05 Table VI).

The levels of IL-10 in the marked effect group before and after treatment were 51.29±5.72 and 25.71±4.18 pg/ml, respectively, and those of the no effect group were 51.23±5.73 and 40.53±4.39 pg/ml, respectively. The two groups had higher IL-10 levels prior to treatment (P<0.05) and the marked effect group had lower IL-10 levels than the no effect group after treatment (P<0.05).

The levels of TNF-α in the marked effect group prior to and after treatment were 405.34±42.38 and 304.72±52.47 ng/ml, respectively, and those of the no effect group were 404.85±48.34 and 373.84±43.10 ng/ml, respectively. The two groups had higher TNF-α levels prior to treatment (P<0.05) and the marked effect group had lower TNF-α levels than the no effect group after treatment (P<0.05). These results are presented in Fig. 2.

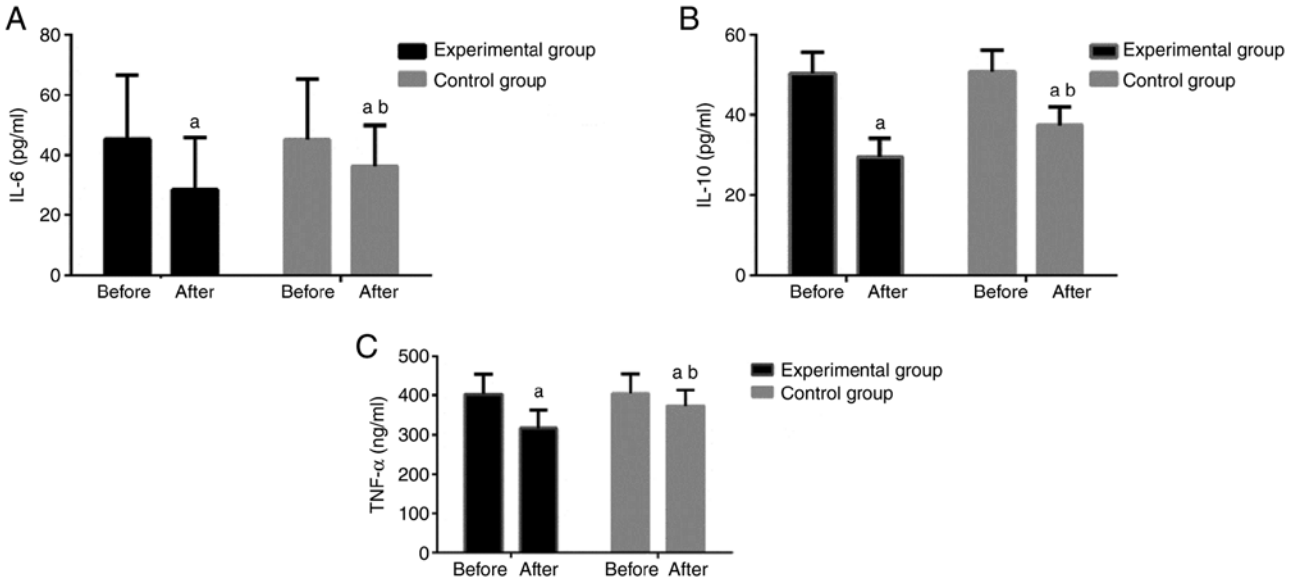

Figure 1. Concentrations of IL-6, IL-10 and TNF-α in the knee synovial fluid from subjects in the control and experimental groups prior to and after treatment. Comparison of the (A) IL-6, (B) IL-10 and (C) TNF-α concentrations in the knee synovial fluid between the control and experimental groups. [a]P<0.05 vs. the control or experimental group before/after treatment; [b]P<0.05 vs. the control group or experimental group after treatment.

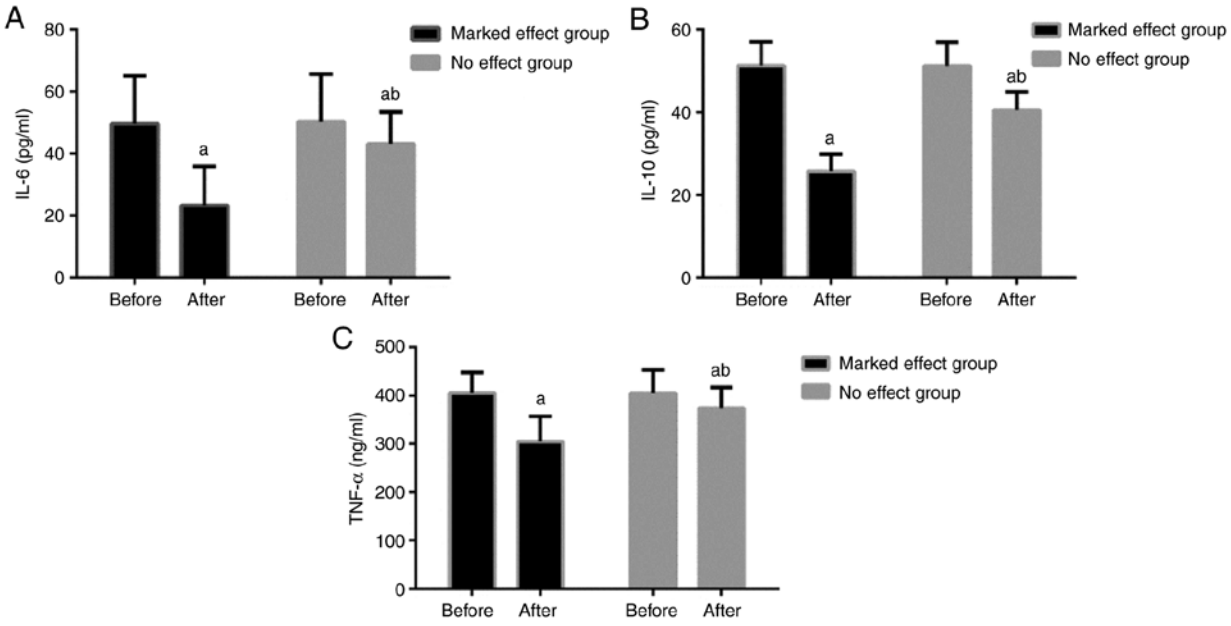

Figure 2. Concentrations of IL-6, IL-10 and TNF-α in knee synovial fluid from subjects in the marked effect and no effect groups prior to and after treatment. Comparisons of the (A) IL-6, (B) IL-10 and (C) TNF-α concentrations in the knee synovial fluid between the marked effect and no effect groups. [a]P<0.05 vs. the control or experimental group before/after treatment; [b]P<0.05 vs. the no effect or marked effect group after treatment.

Discussion

Knee OA is a universally disabling joint disease that is frequently accompanied by severe joint pain, swelling, stiffness and loss of movement (30). It is the major cause of knee joint pain and is usually treated with conservative methods (31-34). The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis recommends NSAIDs as the first choice for the treatment of knee pain, particularly for OA patients who are >75 years of age and patients with complications or increased risks of cardiovascular, gastrointestinal or kidney-related side effects (35). However, for certain patients with renal insufficiency, NSAIDs induce high nephrotoxicity (36), indicating the need for novel therapeutic regimens.

Radiofrequency has been adopted for numerous years to treat diseases associated with neuropathic pain (37). Pulsed radiofrequency is a non-pharmacological treatment that has been indicated to reduce severe chronic joint pain; this safe and minimally invasive treatment may be performed in outpatient settings (38,39). Recent studies have investigated the effectiveness of pulsed radiofrequency in patients with chronic pain who were difficult to treat with conservative methods (40) and found pulsed radiofrequency to be an effective and reliable technique for the palliative treatment of chronic pain

Table V. Evaluation of knee joint function in the two groups at different time-points.

Group	Before treatment	After treatment	t[a]	P-value
Control (n=32)	41.34±7.24	73.31±9.17	21.286	<0.001
Experimental group (n=32)	42.19±7.18	84.24±13.52	18.751	<0.001
t[b]	0.472	3.785		
P-value	0.638	<0.001		

[a]Paired t-test; [b]unpaired t-test. Values are expressed as the mean ± standard deviation.

Table VI. Comparison of IL-6, IL-10 and TNF-α levels between the two groups before and after treatment.

	Experimental group				Control group			
Index	Before	After	t	P-value	Before	After	t	P-value
IL-6, pg/ml	45.31±21.38	28.60±17.27[a]	2.467	0.020	45.21±20.23	36.39±13.43[a,b]	2.452	0.0262
IL-10, pg/ml	50.48±5.23	29.54±4.64[a]	11.56	<0.001	50.86±5.39	37.43±4.59[a,b]	7.982	<0.001
TNF-α, ng/ml	402.14±53.14	316.35±46.53[a]	9.864	<0.001	403.78±52.29	372.71±40.26[a,b]	3.271	0.003

Values are expressed as the mean ± standard deviation. [a]P<0.05 vs. the experimental group before treatment (paired t-test); [b]P<0.05 comparison with the experimental group after treatment (unpaired t-test).

in patients with gonarthritis. However, only a small number of clinical studies (41,42) on repeated intra-articular pulsed radiofrequency for the treatment of knee joint pain have been performed. It has been reported that the expression levels of cytokines, such as IL-1 receptor α, IL-6, IL-8, IL-10, IL-15 and monocyte chemo-attractant protein-1 are increased in the synovial fluid of patients with traumatic anklebone arthritis, due to inflammatory injury (43). However, only a small number of studies (16,44) on the changes in the levels of inflammatory cytokines in the synovial fluid of patients with knee joint pain undergoing repeated treatment with intra-articular pulsed radiofrequency have been performed, which is worth investigating.

The results of the present study revealed that after treatment with intra-articular pulsed radiofrequency, the subjects in the experimental group had a lower VAS and higher total effectiveness rate than those in the control group, while experiencing a higher degree of pain relief and improved knee joint function. This indicated that the efficacy of the treatment in the experimental group was better than that in the control group. Nagar *et al* (45) compared pulsed radiofrequency therapy and continuous radiofrequency therapy in the treatment of patients with facet joint lower back pain and demonstrated that continuous radiofrequency therapy was more effective, which is similar to the results of the present study. In the present study, the subjects in the experimental group had a higher incidence of adverse reactions than those in the control group. It may be hypothesized that the increase in the number of treatments in the experimental group led to an increase in the number of adverse reactions, which suggests that close attention must be paid to whether patients are affected by other diseases during treatment.

After treatment, both groups had decreased concentrations of IL-6, IL-10 and TNF-α in the synovial fluid of the knee joint. The experimental group performed better than the control group with regard to these indexes; the marked effect group had lower concentrations of IL-6, IL-10 and TNF-α than the control group, which was consistent with the results of the study by Li *et al* (46) on the correlation of changes in the serum inflammatory cytokines with knee joint pain symptoms. Their study revealed that the degree of pain was closely related to TNF-α levels. It may be hypothesized that repeated intra-articular pulsed radiofrequency may reduce the inflammatory response and lower the degree of knee pain in patients by inhibiting the expression of IL-6, IL-10 and TNF-α in the synovial fluid. By assessing the duration of pulsed radiofrequency in alleviating neuropathic pain, Ramzy *et al* (47) determined that a prolonged duration of pulsed radiofrequency had a better analgesic effect and that an increase in duration was associated with a significant decrease in IL-6 and TNF-α levels; these results support the present hypothesis that pulsed radiofrequency reduces the production of pro-inflammatory cytokines. Moffett *et al* (48) studied the regulatory mechanism of pulsed radiofrequency energy on peripheral pain and determined that the levels of primary transcription products produced by structural gene pre-mRNA, an endogenous opiate-like substance, and corresponding opioid peptide levels were increased, which further supports the present hypothesis.

The present study confirmed that repeated intra-articular pulsed radiofrequency is a feasible treatment method for patients with knee joint pain based on the comparison of single and repeated treatments. However, there are certain limitations to the present study. For instance, the number of research subjects included in the study was low and all patients undergoing repeated treatment were treated at the same time. The treatment time of the patients was not determined based on their individual conditions; thus, the patients' pain relief was

inconsistent. The patients' age was associated with certain problems, e.g. inflammatory mediator levels in a 47-year-old patient may not be comparable with those of a 60-year-old; however, the median age was similar among groups. Of note, there was a lack of homogeneity during patient selection. In future studies, it will be endeavored to improve the study design and screen patients according to strict inclusion and exclusion criteria in order to obtain more consistent results in the future.

In conclusion, repeated intra-articular pulsed radiofrequency is an effective method for the treatment of knee joint pain with a good analgesic effect and it may be used in clinical practice.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors conceived and designed the study and interpreted the results of the experiments. JZ and ZW performed experiments and analyzed data. HX prepared figures and drafted the manuscript. ZY edited and revised the manuscript, designed the current study and analyzed the data. All authors read and approved the final version of the manuscript. JZ and HX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Caoxian People's Hospital (Caoxian, China) and all research subjects signed an informed consent form.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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