

The Effects and Potential Mechanisms of Moxibustion for Rheumatoid Arthritis-Related Pain: A Randomized, Controlled Trial

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Purpose: To investigate the effects of moxibustion in relieving pain, and other clinical symptoms for patients with rheumatoid arthritis (RA), and explore the potential mechanism of moxibustion treatment for RA.

Patients and Methods: Seventy qualified RA patients were randomly assigned in a 1:1 ratio to the moxibustion group or the routine group. The routine group only took oral methotrexate tablets and folic acid tablets. The moxibustion group was treated with moxibustion based on oral pharmaceutical. Moxibustion was performed two times weekly for 8 weeks, a total of 16 sessions. Patients scored their pain on a visual analog scale (VAS). The American College of Rheumatology improvement criteria of 20%, 50% and 70% (ACR20, ACR50 and ACR70) after treatment were investigated. Clinical symptoms, a disease activity score using 28 joint counts (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), health assessment questionnaire (HAQ), interleukin 1 β (IL-1 β), tumor necrosis factor-alpha (TNF- α), and vascular endothelial growth factor (VEGF) of RA patients were analyzed before and after treatment.

Results: After treatment, the VAS scores, tender and swollen joint counts, morning stiffness scores, disease activity scores (DAS28, SDAI, CDAI), HAQ scores in the two groups were both improved, and the effects of moxibustion group were more obvious ($P < 0.05$). The ACR20 and ACR50 of the moxibustion group were greater than that of the routine group ($P < 0.05$), no significant difference of the ACR70 existed between the two groups ($P > 0.05$). In addition, the decreases of IL-1 β , TNF- α , VEGF of the moxibustion group were better than that of the routine group ($P < 0.05$).

Conclusion: Moxibustion could effectively relieve pain, ameliorate the clinical symptoms, and decrease the disease activity of RA. The potential mechanism may be the decrease in the level of serum inflammatory factors.

Keywords: moxibustion, rheumatoid arthritis, pain, inflammatory factor

Introduction

As a chronic inflammatory disease related to autoimmunity, rheumatoid arthritis (RA) can cause pain, swelling, stiffness of multiple joints, damage of synovium and cartilage.^{1,2} RA affects about 0.5% to 1.0% of the population worldwide. The peak age of incidence is 45–55 years, the prevalence ratio of female and male is about 2–3:1 for RA.³ Because of daily pain, stiffness, and physical disability, RA leads to the decrease of quality of life (QoL) and the increase of psychological burden in patients.^{4–6} Recent study showed approximately 13.5% of RA patients accompanied by anxiety,⁷ which was related to the increase of disease activity and worse QoL.⁸ In addition, RA also has many extra-articular manifestations and complications, such as pulmonary involvement, peripheral neuropathy, cardiovascular disease.^{9–12} RA has proved to be a significant public health-care and social issue because of its lingering disease course, high disability rate, and substantial burden.¹³

RA is mainly treated with pharmacological therapy at present, including disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids. Although the response for most patients is favorable in joint pain and inflammation, many are still suboptimal for the current therapies. Besides, long-term use of these medications is easy to cause adverse effects of liver, kidney, gastrointestinal tract, and cardiovascular system.^{14–17} Accordingly, a complementary and alternative therapy with effective and few adverse events is urgently required.

Moxibustion, as a widely used traditional Chinese medicine therapy, has been applied for thousands of years as non-pharmacological therapy for pain relief in clinical. Several animal experiments have validated the effects of moxibustion for anti-inflammatory, analgesic and detumescence, including regulating inflammatory cytokines, alleviating the cartilage degradation and bone destruction, improving the synovial inflammation hyperemia and edema in RA.^{18–20} Moxibustion on “Zusanli (ST 36)” and “Shenshu (BL 23)” could diminish swelling, reduce the metatarsal circumference, relieve multiple arthritis, lower tumor necrosis factor (TNF), interleukin 1 (IL-1) and nitric oxide (NO) content in adjuvant arthritis rats.²¹ A clinical trial also found that spreading moxibustion had a significant therapeutic effect on RA.²² In two recent meta-analyses, moxibustion combined with western medicine therapy could effectively improve pain in patients with RA.^{23,24} However, there are still few relevant clinical studies comprehensively evaluating the efficacy of moxibustion in treating RA, and the effects of moxibustion on inflammatory factors in RA patients are unclear. We conducted a 9-week two-arm parallel pilot randomized clinical trial to observe the effectiveness and safety for moxibustion, further to explore the potential mechanism of moxibustion treatment for RA.

Patients and Methods

This was a randomized controlled trial. RA patients were recruited from the outpatient department of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (CDUTCM) from March 2017 to January 2019. All subjects signed the informed consent.

Participants

Patients were enrolled if they fulfilled all of the following criteria: (1) matched the diagnosis criteria for RA based on the 2010 American College of Rheumatology and the European League Against Rheumatism classification criteria²⁵; (2) aged 18 to 65 years; (3) were with DAS28 >3.2; (4) did not use glucocorticoid drugs and other antirheumatic pharmaceutical within 24 weeks; (5) had not participated in any other clinical trials.

Patients were excluded if they had any following conditions: (1) were with unclear conscious and unable to cooperate with the investigator to complete the study or diagnosed with mental disorders; (2) were in an advanced stage with IV joint function; (3) suffered from other autoimmune diseases; (4) complicated by malignant tumors or severe disorders in heart, brain, liver, kidney, lung; (5) were pregnant or lactating; (6) had contraindications to moxibustion (eg, scar or allergic constitution).

Randomization and Blinding

After a 1-week baseline period, the qualified RA patients were randomly assigned in a 1:1 ratio to the moxibustion group or the routine group, with a computer-generated randomization sequence generated by SPSS 21.0 statistical software package. The sealed and opaque envelopes were used to seal the randomization sequence. The entire randomization process was performed by an individual coworker. Because of the nature of the intervention, acupuncturists could not be blinded. Data collection and data analysis was performed blinded.

Interventions

The Routine Group

Patients only received conventional pharmaceutical therapy for 8 weeks as recommended by the guidelines,²⁶ including 7.5mg methotrexate and 10 mg folic acid (took orally, once a week).

The Moxibustion Group

Patients received moxibustion treatment in addition to pharmaceutical therapy. Moxibustion was performed on bilateral ST36, bilateral BL23 and A-Shi points (Figure 1). The acupoints were localized according to the WHO Standard Acupuncture Locations. ST36 located 3 cun directly below ST35 (Dubi), and one-digit lateral to the anterior margin of the tibia. BL23 located the same level of the second subspinous of lumbar vertebra, and 1.5 cun lateral to the posterior midline on the back. A-Shi points in this study were the evident tender points of the pain joints. These acupoints selection was based on some experimental study,^{19,20} experience from clinical experts and our previous study.²⁷ Wheat-grain moxibustion, one of the direct moxibustion, was applied on ST36 and A-Shi points at small joints of limbs. BL23 was treated with salt-separated moxibustion. A-Shi points at large joints was treated with moxibustion on ginger.

Acupuncturists used moxa wool (Yilejia Moxa Co., Nanyang, China) to process small moxa cone (3mm of diameter and height) and large moxa cone (10mm of diameter and height) (Figure 2A), then labelled acupoints with markers. The acupuncturists applied Vaseline above ST36 and A-Shi points in small joints of limbs to stick the small moxa cones, then light the small moxa cones by line incenses. When patients felt hot, the acupuncturists removed the small moxa cone immediately to avoid burn. Five small moxa cones were burnt at per acupoint for each time (Figures 2B and 2C). A-Shi points at large joints were applied with moxibustion on ginger (Figures 2D and 2E), the acupuncturists lighted the moxa cone and then put it at a cut ginger on A-Shi points. Once the moxa cone was burned out and the patients had a sense of hot, replaced another moxa cone, three large moxa cones were burnt at per acupoint for each time. For BL23, the acupuncturists put a piece of sterile gauze with an appropriate amount of salt on the BL23 points area, then placed the large moxa cones and lit them. When patients felt hot, replaced the moxa cones, six large moxa cones were burnt every time (Figure 2F).

Patients in the moxibustion group received 16 sessions of moxibustion treatment (twice per week, a total of 8 weeks). All moxibustion treatments were operated by licensed acupuncturists, who were trained with how to locate acupoints, make moxa cone, and complete the moxibustion operation according to the standard.

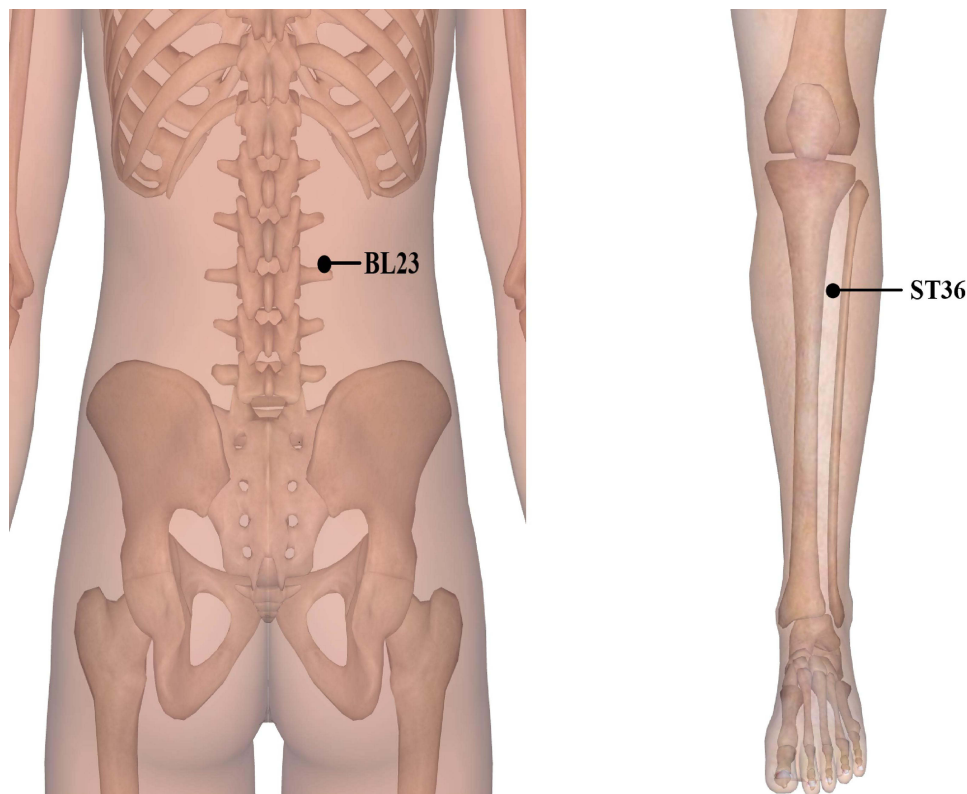


Figure 1 The acupoints used in this trial.

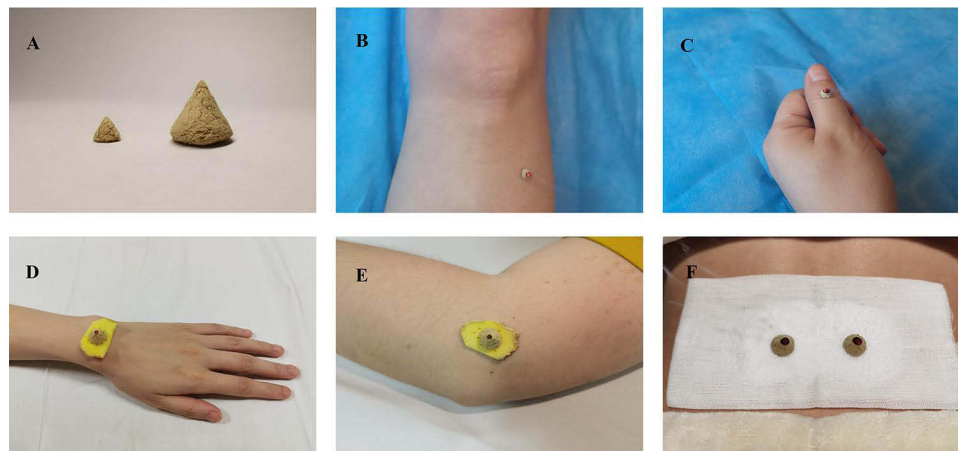


Figure 2 Schematic diagram of the moxibustion. (A) Samples of moxa cones; (B and C) Wheat-grain moxibustion; (D and E) Moxibustion on ginger; (F) Salt-separated moxibustion.

Outcome Measurements

The pain of joints was measured by a horizontal visual analog scale (VAS) ranging from 0 to 10, where higher scores indicate greater pain.^{28,29} The other outcomes included tender and swollen joint counts, morning stiffness scores (evaluated the morning stiffness duration, 0 point: asymptomatic, 2 points: <1 hour, 4 points: 1–2 hours, 6 points: >2 hours). In addition, 28 joint counts along with other components (DAS28), simplified disease activity index (SDAI) and clinical disease activity index (CDAI) reflected the disease activity (higher is worse).^{30–34} The QoL of patients was evaluated through health assessment questionnaire (HAQ).³⁵ The clinical response was measured using the American College of Rheumatology (ACR) improvement criteria, including improvements of 20%, 50% and 70% (ACR20, ACR50 and ACR70 responses),³⁶ the ACR evaluation system was accepted as an international standard for evaluating clinical therapeutic effect of RA. The levels of serum inflammatory factors including interleukin 1 β (IL-1 β), tumor necrosis factor-alpha (TNF- α), vascular endothelial growth factor (VEGF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were measured before and after treatment.

Calculation of Sample Size and Statistical Analysis

According to our previous pilot study, after treatment, the mean VAS score of RA patients in the moxibustion group was 4.0 points and the standard deviation was 1.28 points, while the mean VAS score of RA patients in the routine group was 5.4 points and the standard deviation was 1.9 points. This study was set up according to the ratio of 1:1 to test the level $\alpha=0.05$, inspection efficiency $1-\beta=0.95$. The sample size was estimated using t tests in G*Power (version 3.1.7, Franz Faul, University Kiel, Germany). Through calculation, the comprehensive effect size was 0.864. It was estimated that the total number of samples required in the two groups was 60. To compensate for a 15% attrition rate, the sample size expanded to 35 patients in each group, a total of 70 cases were required.

Statistical analysis was calculated with SPSS 21.0 by a blinded evaluator. Categorical data were described as number and percentages (n%), and compared using the chi-squared (χ^2) test. *T*-test and nonparametric tests were used for normally distributed quantitative variables and skewed quantitative variables, respectively. Pearson correlation coefficients were employed for nonnormal distribution data for correlation analysis. *P* value <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 101 RA patients were screened, 70 patients were eligible and randomized, but only 66 patients completed 8 weeks of treatment (Figure 3). Baseline data included gender, age, family history, education level, body mass index

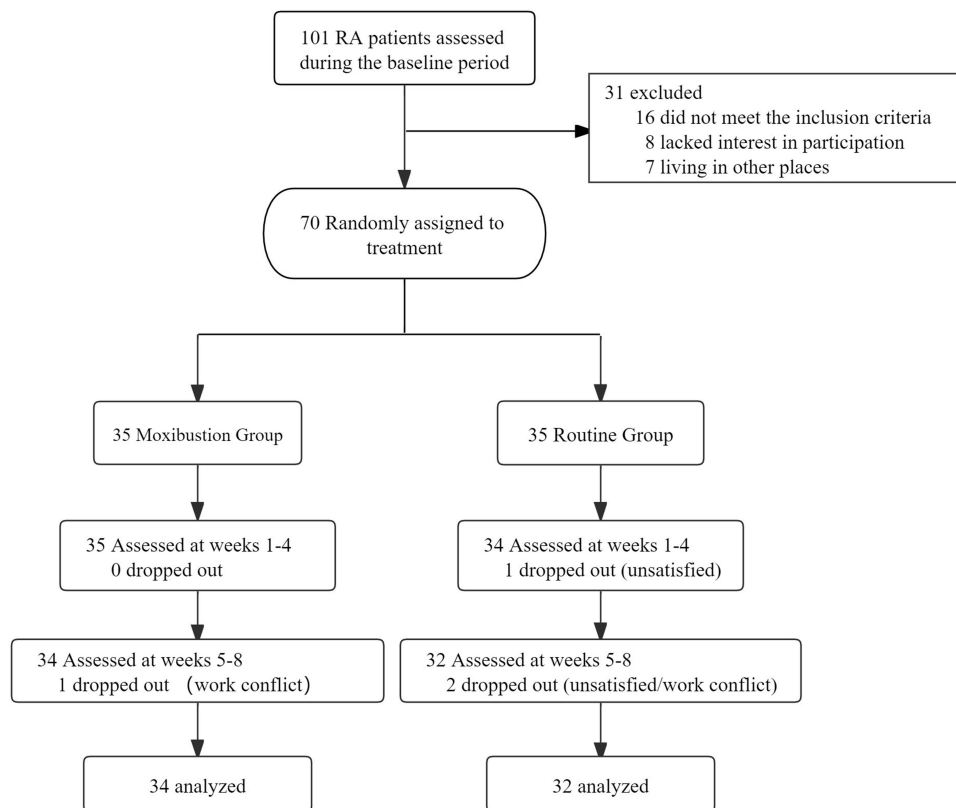


Figure 3 Flowchart of screening, enrollment, randomization, and treatment.

(BMI), resting blood pressure, and duration of illness. No remarkable differences in baseline data were found between the two groups (Table 1).

The Therapeutic Effects in the Two Groups

Significant improvements were observed for most clinical outcome measurements after treatment between the two groups (Table 2). The VAS scores, tender and swollen joint counts, morning stiffness scores of the moxibustion group were

Table 1 The Baseline Characteristics in the Two Groups

Characteristic	Moxibustion Group (N=34)	Routine Group (N=32)	P value
Women, n (%)	31 (91.2)	28 (87.5)	0.932
Age (years), Mean ± SD	47.3 ± 10.5	48.2 ± 9.9	0.723
BMI, Mean ± SD	20.6 ± 2.4	21.3 ± 2.9	0.244
Family history, yes, n (%)	5 (14.7)	3 (9.4)	0.775
Educational level, n (%)			0.132
Primary education or less	4 (11.8)	5 (15.6)	
Secondary education	10 (29.4)	16 (50.0)	
Tertiary education	20 (58.8)	11 (34.4)	
Resting blood pressure, Mean ± SD, mm Hg			
Systolic	119.8 ± 3.2	119.5 ± 4.7	0.488
Diastolic	76.6 ± 5.2	78.5 ± 4.6	0.121
Duration of illness (years), Mean ± SD	7.63 ± 7.24	6.23 ± 6.13	0.403

Notes: The data of gender, family history, and educational level were calculated using the χ^2 test. Other data was calculated using independent *t*-test.
Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 2 Comparison of the Therapeutic Effects Between the Two Groups

Items	Moxibustion Group	Routine Group	P value
VAS score			
Baseline	6.56 ± 1.46	6.69 ± 1.66	0.738
End of treatment	3.32 ± 1.65	4.72 ± 1.92	0.002**
Tender joint counts (28)			
Baseline	13.47 ± 7.80	13.75 ± 6.97	0.879
End of treatment	6.15 ± 5.00	10.25 ± 7.22	0.011*
Swollen joint counts (28)			
Baseline	8.97 ± 6.13	8.78 ± 6.26	0.797
End of treatment	3.09 ± 3.04	6.53 ± 6.49	0.042*
Morning stiffness score			
Baseline	3.29 ± 1.96	3.25 ± 1.67	0.989
End of treatment	1.32 ± 1.27	2.44 ± 1.66	0.005**
DAS28			
Baseline	5.99 ± 1.20	5.98 ± 1.01	0.961
End of treatment	4.40 ± 1.26	5.19 ± 1.39	0.017*
SDAI			
Baseline	51.93 ± 37.87	56.68 ± 34.40	0.596
End of treatment	24.66 ± 14.61	33.37 ± 17.60	0.032*
CDAI			
Baseline	35.13 ± 14.24	36.13 ± 12.59	0.766
End of treatment	16.77 ± 9.17	26.34 ± 14.25	0.003**
HAQ			
Baseline	0.51 ± 0.37	0.43 ± 0.33	0.374
End of treatment	0.19 ± 0.18	0.31 ± 0.28	0.041*

Notes: Data are Mean ± SD, and were calculated using independent t-test; * $P < 0.05$; ** $P < 0.01$.

Abbreviations: VAS, visual analog scale; DAS28, a disease activity score using 28 joint counts along with other components; SDAI, simplified disease activity index; CDAI, clinical disease activity index; HAQ, health assessment questionnaire.

significantly less than those in the routine group at week 8 ($P < 0.05$). The changes of SDAI, CDAI and DAS28 in the moxibustion group from baseline to week 8 were greater compared with the routine group ($P < 0.05$). At baseline, mean HAQ scores were similar for patients between the two groups. At week 8, mean HAQ scores in the moxibustion group were lower than that in the routine group ($P < 0.05$).

The ACR20 response rate was 79.4% (95% CI, 65.1–93.7%) in the moxibustion group and 53.1% (95% CI, 34.8–71.4%) in the routine group. The ACR20 response rate in the moxibustion group was higher than the routine group ($P = 0.024$; Table 3). The ACR50 and ACR70 response rates of the moxibustion group were reached by 41.2% and 14.7% at week 8. In the routine group, the ACR50 and ACR70 response rates were 15.6% and 3.1%, respectively. The proportion of patients achieving ACR50 response rates in moxibustion group was significantly higher than that in the routine group ($P < 0.05$). No significant difference in ACR70 response rates was observed between the two groups ($P > 0.05$; Table 3).

Table 3 Treatment Response Rates of RA Patients in the Two Groups

Items	Moxibustion Group	Routine Group	P value
ACR20	27 [79.4 (65.1–93.7)]	17 [53.1 (34.8–71.4)]	0.024*
ACR50	14 [41.2 (23.7–58.6)]	5 [15.6 (2.3–28.9)]	0.022*
ACR70	5 [14.7 (2.2–27.2)]	1 [3.1 (–3.2–9.5)]	0.102

Notes: Data are presented as percentages with their 95% CIs, P values based on χ^2 test between the two groups. *, $P < 0.05$.

Abbreviations: ACR20, ACR50 and ACR70, The American College of Rheumatology improvements criteria of 20%, 50% and 70%.

RA-Associated Serum Inflammation Markers

No significant between-group differences were observed in ESR and CRP levels after treatment ($P>0.05$). The moxibustion group had greater improvement in mean IL-1 β , TNF- α , and VEGF levels at week 8 ($P<0.05$; Table 4).

Correlation Among the Different Indicators After Treatment

IL-1 β showed a positive correlation with HAQ, TNF- α , and VEGF. TNF- α had a positive correlation with DAS28, HAQ, and VEGF. VEGF showed a positive correlation with VAS score, DAS28, and HAQ ($P<0.05$; Table 5).

Safety

Two patients in the moxibustion group were reported for moxibustion-related adverse reaction, including burn and blister. All AEs were reported as mild, and none of them required for special medical interventions. The two patients fully recovered from the AEs and remained in the trial.

Table 4 Change in Serum Inflammatory Factor Level of the Two Groups

Items	Moxibustion Group	Routine Group	P value
ESR (mm/h)			
Baseline	52.85 \pm 30.20	53.66 \pm 31.37	0.916
End of treatment	38.47 \pm 26.92	41.88 \pm 27.36	0.612
CRP (mg/L)			
Baseline	16.80 \pm 29.70	20.56 \pm 29.27	0.559
End of treatment	7.90 \pm 8.40	7.06 \pm 7.31	0.668
IL-1 β (pg/mL)			
Baseline	30.75 \pm 16.31	33.52 \pm 16.34	0.493
End of treatment	21.75 \pm 10.61	28.56 \pm 15.69	0.042*
TNF- α (pg/mL)			
Baseline	27.66 \pm 14.12	32.43 \pm 16.01	0.204
End of treatment	20.60 \pm 12.09	27.07 \pm 13.41	0.043*
VEGF (pg/mL)			
Baseline	87.43 \pm 47.65	109.84 \pm 55.74	0.083
End of treatment	66.27 \pm 33.46	91.18 \pm 47.49	0.016*

Notes: Data are Mean \pm SD, and were calculated using independent t-test; * $P < 0.05$.

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-1 β , interleukin 1 β ; TNF- α , tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

Table 5 Correlation Among the Different Indicators After Treatment

Items	Items	r	P value
IL-1 β	HAQ	0.274	0.026*
	TNF- α	0.641	0.000**
	VEGF	0.633	0.000**
TNF- α	DAS28	0.249	0.044*
	HAQ	0.346	0.004**
	VEGF	0.435	0.000**
VEGF	VAS score	0.352	0.004**
	DAS28	0.283	0.021*
	HAQ	0.377	0.002**

Notes: Data were calculated using Pearson correlation coefficient. * $P < 0.05$; ** $P < 0.01$.

Discussion

RA is an inflammatory disease involving the autoimmune system with complicated etiology and pathogenesis, which cannot be cured, and even brings heavy economic and medical burden. Moxibustion, as one of the important integral parts of TCM, has been used in treating arthralgia for thousands of years. It contains direct moxibustion (applied the moxa cone directly on the skin) and indirect moxibustion (applied the moxa cone indirectly on the skin through insulating materials). A variety of studies found that both the two moxibustion treatments had significant anti-inflammatory effects on rabbits with RA.^{37,38} Our study combined the two methods of moxibustion, which could effectively relieve local pain of the joints and regulate systemic immunity. At the same time, the direct moxibustion on ST36 and the salt-separated moxibustion on BL23 can also replenish qi, nourish blood, reinforce kidney and warm Yang. Previous studies indicated that moxibustion on ST36 and BL23 had promising antiarthritic effects,¹⁸ and stimulating A-Shi points could play an analgesic role.^{39,40} Therefore, the three acupoints were selected in this study, embodied the principle of treating both symptoms and root causes.

In terms of improving VAS score, moxibustion group had better effect than routine group, and similar results were also observed in the tender and swollen joint counts. The warm stimulation of moxibustion can dilate blood vessel, increase local blood flow, improve microcirculation to relieve swelling and pain.^{41,42} Except for pain, morning stiffness is also one of the main symptoms that accompany the progression of RA. The longer morning stiffness and the more severe pain are associated with the worse condition.⁴³ In this study, moxibustion combined with pharmaceutical had a good effect on improving morning stiffness of RA patients. Moreover, compared with routine group, moxibustion group had greater improvements in DAS28, SDAI, and CDAI, indicating that the combination was more effective than drug therapy alone in reduction of disease activity. In addition, improvements of QoL were also found, based on the HAQ scores, which was related to relief of symptoms and signs. Although moxibustion methods are different, other studies have also shown that moxibustion combined with western medication can effectively decrease the VAS, HAQ and DAS28 scores.⁴⁴⁻⁴⁶ The ACR20 and ACR50 also reflected that the overall effectiveness of moxibustion group was better than routine group. The results of this study suggested that moxibustion plus conventional pharmaceutical therapies were more effective than the use of drugs alone. Our study was congruent with a previous meta-analysis that demonstrated moxibustion plus pharmaceutical therapy were more effective than the pharmaceutical therapy alone in the treatment of RA, especially in relieving pain.²³ Thus, results of this study demonstrated that moxibustion could improve the degree of the curative effect, and had a clinically meaningful benefit in decreasing pain, swelling, morning stiffness in RA patients.

Proinflammatory cytokines (TNF- α , IL-1 β) and VEGF contribute to inflammatory pain.⁴⁷⁻⁴⁹ In addition, IL-1 β and TNF- α can cause joint synovial hyperplasia and hypertrophy, aggravate synovial inflammation, erode cartilage, and joint damage.^{50,51} VEGF promotes angiogenesis and proliferation of inflammatory synovial tissue, affects joint function.⁵² Some studies have identified high levels of TNF- α , IL-1 β and VEGF expression in synovial fluid and plasma of RA patients, and have a positive correlation with ESR, CRP.⁵³⁻⁵⁶ Therefore, decreasing the level of inflammatory factors is crucial in treating RA. In this study, significantly decreases in the levels of serum IL-1 β , TNF- α and VEGF of RA patients after moxibustion were found. The correlation analysis showed that IL-1 β , TNF- α and VEGF were correlated with VAS score, HAQ, DAS28. With the reduction of IL-1 β , TNF- α and VEGF, pain and disease activity also decreased, the patient's physical function improved. Therefore, the decrease of the level of serum inflammatory factors may be the mechanism for analgesia and improvement the clinical symptoms of moxibustion. The results were consistent with a systematic review which indicates that moxibustion can protect the synovium of joint in animal models with RA by downregulation of the level of proinflammatory cytokines.⁵⁷ Moxibustion has a suppressive action on the mediators of inflammation.

The findings of the current study demonstrated that moxibustion combined with pharmaceutical therapy on RA was more effective than monotherapy. Moxibustion showed an advantage in the treatment of RA, not only significantly alleviated the joint pain but also improved patients' QoL. In addition, the incidence of adverse events was low, suggesting that moxibustion was an operable, convenient, effective and safe adjunctive treatment of RA.

Limitations

There were some limitations in this study. Firstly, the sample size is relatively small. Secondly, due to the lack of follow-up, the long-term efficacy remains unclear. In the future studies, we will focus on the long-term effects of the moxibustion on inflammatory mechanisms of RA-related pain.

Conclusion

After a comprehensive comparison of the outcome indicators of the two groups, moxibustion combined with pharmaceutical therapy could significantly relieve pain, decrease the disease activity, ameliorate the clinical symptoms, improve the QoL and overall effective rate of RA patients. Moreover, moxibustion could significantly decrease the level of serum inflammatory factors to achieve anti-inflammatory and analgesic effect.

Abbreviations

RA, rheumatoid arthritis; QoL, quality of life; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; CDUTCM, Chengdu University of Traditional Chinese Medicine; DAS28, a disease activity score using 28 joint counts along with other components; VAS, visual analog scale; ACR20, ACR50 and ACR70, the American College of Rheumatology improvements criteria of 20%, 50% and 70%; SDAI, simplified disease activity index; CDAI, clinical disease activity index; HAQ, health assessment questionnaire; IL-1 β , interleukin 1 β ; TNF- α , tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BMI, body mass index.

Data Sharing Statement

All data generated or used during the study appear in the submitted article. No further data will be shared.

Ethics Approval and Informed Consent

The study was performed according to the principles of the Declaration of Helsinki, approved by the Ethics Committee of the Affiliated Hospital of CDUTCM (NO.2015KL-015), and registered at the Clinical Trial Registry (registration number: ChiCTR-IOR-17012282). Only patients signed the informed consent form were included.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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