

Moxibustion therapy guided by midnight-noon ebb-flow theory on Chinese patients with ankylosing spondylitis: a quasi-experimental study

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Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by National Natural Science Foundation of China (No. 81904274).

Abbreviations

MNEF, midnight-noon ebb-flow; AS, ankylosing spondylitis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; IL-6, interleukin-6; IL-17, Interleukin-17; TNF- α , tumor necrosis factor- α ; axSpA, axial spondyloarthritis; HRQoL, health-related quality of life; CAM, complementary and alternative medicine; CPG, clinical practice guideline; CACM, China Association of Chinese Medicine; SD, standard deviation; ASQoL, ankylosing spondylitis quality of life questionnaire; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs; CRP, C-reactive protein; ANOVA, analysis of variance; CIA, collagen-induced arthritis.

Citation

Yan M, Hua LJS, Zhou X, Xu X. Moxibustion therapy guided by Midnight-Noon Ebb-Flow theory on Chinese patients with ankylosing spondylitis: a quasi-experimental study. *Microenviron Microecol Res.* 2022;4(2):11. doi: 10.53388/MMR2022011.

Executive editor: Na Liu.

Received: 01 April 2022; Accepted: 22 June 2022; Available online: 24 June 2022.

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Abstract

Objective: This study aimed to evaluate the effectiveness of midnight-noon ebb-flow (MNEF) theory guided moxibustion therapy for ankylosing spondylitis (AS) in terms of physical function, disease activity, health-related quality of life, inflammatory cytokines, and immune function biomarkers. **Methods:** 135 AS patients in Changzhou No. 2 hospital affiliated to Nanjing Medical University were randomly allocated to the control group, Moxibustion I group or the Moxibustion II group. AS patients in the control group received conventional intervention alone, while AS patients in the Moxibustion I group and Moxibustion II group received 4-week conventional moxibustion and MNEF theory-guided moxibustion therapy, respectively. Physical function, disease activity, health-related quality of life, inflammatory cytokines, and immune function biomarkers were assessed at baseline and at the endpoint week. **Results:** After moxibustion intervention, only performance of physical function measured by Bath Ankylosing Spondylitis Functional Index (BASFI) ($F = 17.1$, $P < 0.01$), and disease activity by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ($F = 17$, $P < 0.01$) were statistically significant differences between the three groups, and the Bath Ankylosing Spondylitis Metrology Index (BASMI) score were no group differences ($F = 3.15$, $P = 0.07$). The effect of MNEF-theory based moxibustion was shown to be better than conventional moxibustion therapy in the level of erythrocyte sedimentation rate (ESR) (2.67, 95% CI, 0.15 to 5.18; $P = 0.04$) and the ratio of CD4⁺CD25⁺CD127 low (-2.83, 95% CI, -4.68 to -0.98; $P < 0.01$). However, with the use of the Tukey multiple comparisons test, compared with the conventional moxibustion therapy alone, MNEF-theory based moxibustion therapy had no statistically significant improvement in the serum levels of interleukin-6 (IL-6), interleukin-17 (IL-17), tumor necrosis factor α (TNF- α) ($P > 0.05$). **Conclusion:** Overall, MNEF-theory guided moxibustion therapy significantly improved physical activity and health-related quality of life, reduced disease activity, and decreased systemic inflammation for AS patients.

Keywords: ankylosing spondylitis; moxibustion; MNEF theory

Introduction

Ankylosing spondylitis (AS), also known as axial spondyloarthritis (axSpA), is a chronic, systemic, and progressive autoimmune disease of unknown causes that predominantly influences patients' sacroiliac, axial joints, and even extra-articular structures (gut, eyes, skin, kidney, heart, etc.) [1]. It is typically characterized by sacroiliitis, enthesitis, axial inflammation, and new bone formation. The prevalence rate of ankylosing spondylitis in the United States of America is estimated at 0.55%, with an average age of onset of less than 40 years, and in mainland China is likely to be approximately 0.2%–0.3% [2–4]. According to a prior survey from Hong Kong, the average annual medical costs of AS patients are estimated as high as \$ 9,120, with about \$ 3,467 accounting for direct healthcare expenses. Additionally, AS adversely influences the working performance of patients and increases the substantial pressure on family caregivers, healthcare systems, and society. AS can affect patients' daily casual life activities and decrease their health-related quality of life (HRQoL) [5–8]. According to recent international guidelines, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and TNF inhibitors are the most important option for the management of AS [9]. However, NSAIDs were frequently associated with cardiovascular and gastrointestinal risk increasing [10]. DMARDs may only have a partial effect on treating peripheral manifestations of AS patients [11]. Although biological agents showed magic efficacy for AS patients, the cost of these agents was too expensive for Chinese patients [12].

Given these limitations of conventional therapeutic strategies, complementary and alternative medicine (CAM) has attracted attention in both indunon-industrialized-industrialised countries as a valuable, affordable, and relatively safe treatment regimen that may be an adjunct in the conventional Western medicine of AS [13]. Moxibustion, as one of the important CAM has been widely used in treating many rheumatism immunity diseases in China [14, 15]. It is described as a process that utilizes a heat source that is generated by burning *Artemisia* herb to stimulate acupuncture points over the skin, accompanying a feeling of De Qi. From TCM perspectives, AS belongs to the category of *Bi* syndrome in terms of the Chinese Yin-yang and Zang-fu theories. Moxibustion may exert potentially beneficial effects by warming channels and meridians, correcting unbalanced Qi energy, promoting blood circulation and removing blood stasis for patients with AS. Furthermore, acupuncture and moxibustion have been explicitly identified as a recommended complementary therapy option in the latest clinical practice guideline (CPG) for the diagnosis and treatment of *Bi* syndrome (known as rheumatic diseases), which was formulated by the China Association of Chinese Medicine (CACM). Moreover, the previous systematic review had revealed that moxibustion could relieve the pain, reduce the disease activity, and improve the physical function and health-related quality of life (HRQoL) of AS patients [16].

The midnight-noon ebb-flow theory (MNEF) uses flowing water to describe the circulation and infusion of human Qi and blood in the meridians, which originated from the Heavenly Stems and the Earthly Branches. In line with the “biological clock theory,” the MNEF theory belongs to the category of time medicine theory of TCM. That is a day can be divided into 12 ShiChen (24 hours). At the same time, it will also change with the change of time, that is, when Qi and blood are in full bloom, the acupuncture points will open and when Qi and blood are in decline, the acupuncture points and meridians will close. With the help of constant warm stimulation of moxibustion, the effective drug components of *Artemisia* herb can flow into the kidney meridian with the operation of Qi and blood, and play the role of anti-inflammatory, improving immunity, warming meridians, dispersing cold, and relieving pain, to improve the stiffness of patients with AS.

Therefore, this study aimed to evaluate the effectiveness of MNEF-theory guided moxibustion therapy for AS in terms of physical function, disease activity, health-related quality of life, inflammatory cytokines, and immune function biomarkers.

Experimental Section

Ethics statement, trial registration, and the study protocol

This is a prospective, randomized clinical trial performed at Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University following the Declaration of Helsinki [17]. This clinical trial was approved by the hospital ethics committee ([2018] YK006-01) and the registration number was (AMCTR-IPR-18000206). The trial design followed SPIRIT 2013 [18] and the CONSORT statement [19]. All participants signed informed consent before joining the present study.

Participants

Inclusion criteria were: (1) Participants were diagnosed as AS [20]; (2) Early and medium-term AS patient of grade I-III sacroiliitis; (3) Age between 18 and 70 years; (4) Stable on the base drug regimen (NSAIDs and DMARDs) for at least 1 month; (5) Participate in the intervention treatment for one month and sign the informed consent form. Exclusion criteria: (1) Pregnant or lactating women; (2) AS patient of grade IV sacroiliitis; (3) with serious complications; (4) Allergic to meloxicam and sulfasalazine; (5) Combined with serious diseases.

According to the sample size calculation with the G*Power tool, we referred to the previous moxibustion case report under the BASFI as the primary outcome. The parameters were set as follows: $\alpha = 0.05$, power $(1-\beta) = 0.9$, mean difference = -0.65, standard deviation (SD) = 1. Thus, a total of 112 patients with AS were included in this study. Considering a 20% loss to follow-up, finally, 135 AS patients attending the hospital, from March 2018 to December 2021 were included [21]. As shown in Figure 1, 135 qualified patients were randomly assigned to three groups with a 1:1:1 ratio [control group (n = 45), moxibustion I group (n = 45) or the moxibustion II group (n = 45)]. The random allocation number was concealed in opaque and sealed envelopes. AS patients in the control group received conventional intervention alone (NSAIDs and DMARDs therapy according to the ASAS guideline), AS patients in the moxibustion I group received moxibustion therapy. Whereas, AS patients in the moxibustion II group received MNEF-theory guided moxibustion intervention.

Intervention process

According to the principles of this theory, Yin can achieve its most levels at Midnight time (23-1); whereas, Yang reaches its most levels at Noon time (11-13). AS is mostly manifested as a kidney-meridian related disease in TCM, and You hour (17:00-19:00) is the main time for renal function. Kidney Qi and blood are the most vigorous at the You hour (17:00-19:00), and at this time the human body enters the stage of kidney essence (the essence of the viscera), which is beneficial to store the essence of the kidney for the whole day. Therefore, the MNEF theory is adopted to select the (17:00-19:00) to perform the moxibustion intervention. The governor's meridian and the Mingmen (Du 4) and Shenshu (BL 23) acupuncture points on the bladder meridian of the foot Taiyang were selected as the main meridian and acupuncture points.

In the Moxibustion I group, firstly, TCM nursing practitioners evaluated and checked the Rheumatology physician's orders, and assessed the skin condition. Moreover, TCM nursing practitioners checked the patients' past history, current symptoms, location of arthritis, the patients' age, educational level, and current psychological state. Before moxibustion intervention, TCM nursing practitioners should prepare a treatment plate, moxibustion, matches, and towel if necessary. During the moxibustion process, TCM nursing practitioners bring all the supplies to the bedside, explain and check the patients' information again. Next, TCM nursing practitioners help AS patients to take a reasonable body position and pay attention to exposing the moxibustion site. Moreover, TCM nursing practitioners implement moxibustion according to the patients' condition or Rheumatology physician's orders at any time. TCM nursing practitioners should locate four acupuncture points (ShenShu BL23, MingMen Du 4, Yaoyangguan Du 3, and 'Ashi' acupuncture points), then TCM nursing practitioners ignite the moxibustion strip, and carry

out moxibustion at about 2 cm to 3 cm away from the skin of the acupuncture points [21-24]. It is appropriate to have a local sense of warmth without burning pain for AS patients. Generally, moxibustion at each acupuncture point lasts for 10 minutes (the total time of moxibustion intervention was 40 minutes) until the local skin is red [25, 26]. TCM nursing practitioners would ask AS patients if there was burning pain during moxibustion intervention and prevent burning at any time. In the process of moxibustion intervention, the TCM nursing practitioners should ask the patient whether there was burning pain at any time, and adjust the moxibustion distance in time to prevent burns. Moreover, the TCM nursing practitioners monitor the disease condition and whether there was body pain caused by body position discomfort. TCM nursing practitioners should also understand the physiological and psychological feelings of AS patients. During the moxibustion intervention, the moxibustion ash produced by moxibustion sticks should be moved away from the plate in time to prevent skin burned and clothing burned. After moxibustion, extinguish the moxa fire of moxibustion immediately. After cleaning patients' local skin, TCM nursing practitioners assisted the patient in dressing, placed the patient in a comfortable lying position, and opened the window for ventilation. After moxibustion intervention, TCM nursing practitioners would take a health education to AS patients: after moxibustion, the local skin is slightly red and hot, which is a normal phenomenon. If there are small blisters after moxibustion, they can be absorbed by themselves without intervention. If the blister is large, the liquid in the blister can be extracted with a sterile syringe, covered with sterile gauze, and kept dry to prevent infection. AS patients in the Moxibustion II group received the same moxibustion process as Moxibustion I group, but the intervention time was fixed in the tenth earthly branch (You time 5:00-7:00 p.m.). AS patients in the control group only received medications, exercise, and health care education programs.

Outcomes

(1) The primary outcomes: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) were used for evaluating the physical function of AS before and after moxibustion intervention [27, 28].

(2) The secondary outcomes: ankylosing spondylitis quality of life

questionnaire (ASQoL) was also applied to assess AS-related quality of life before and after moxibustion intervention [29].

(3) Laboratory tests: ESR, CRP, IL-6, IL-17, TNF- α , CD4⁺CD25⁺CD27 low Treg.

Statistical methods

The statistical analysis was carried out by the SPSS 18.0. The continuous normally distributed variables including BASDAI, BASFI, BASMI, ASQoL, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), IL-6, IL-17, and TNF- α were compared by one way analysis of variance (ANOVA). A value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 135 participants were recruited for this research. Of these, 129 (Control group $n = 45$, Moxibustion group I $n = 43$, Moxibustion group II, $n = 41$) completed and returned all follow-up measures (Figure 1). There was no significant difference between the groups in the baseline data ($P > 0.05$) (Table 1).

BASFI, BASDAI, BASMI, ASQOL, and laboratory examinations of AS

BATH scores and ASQoL Only physical function measured by BASFI ($F = 17.1$, $P < 0.01$), and disease activity by the BASDAI ($F = 17$, $P < 0.01$) were significant differences between the three groups, and the BASMI score were no group differences ($F = 3.15$, $P = 0.07$). Moreover, the effect of MNEF-theory based moxibustion was shown to be better than conventional moxibustion therapy in the mean score of the BASFI index (5.67, 95% CI, 1.08 to 10.25; $P = 0.02$) and mean score of the BASDAI index (between-group difference was 0.25, 95% CI, 0.04 to 0.66; $P = 0.03$). (Figure 2).

There was a significant difference between the three groups of moxibustion I, Moxibustion II, and control in terms of ASQoL after the intervention ($F = 60$, $P < 0.01$). In addition, Tukey multiple comparisons test indicated that compared with the conventional moxibustion therapy alone, MNEF-theory based moxibustion had a greater improvement in ASQoL with between-group differences of 2.67 (95% CI, 0.91-4.43; $P < 0.01$) at week 6 (Figure 2).

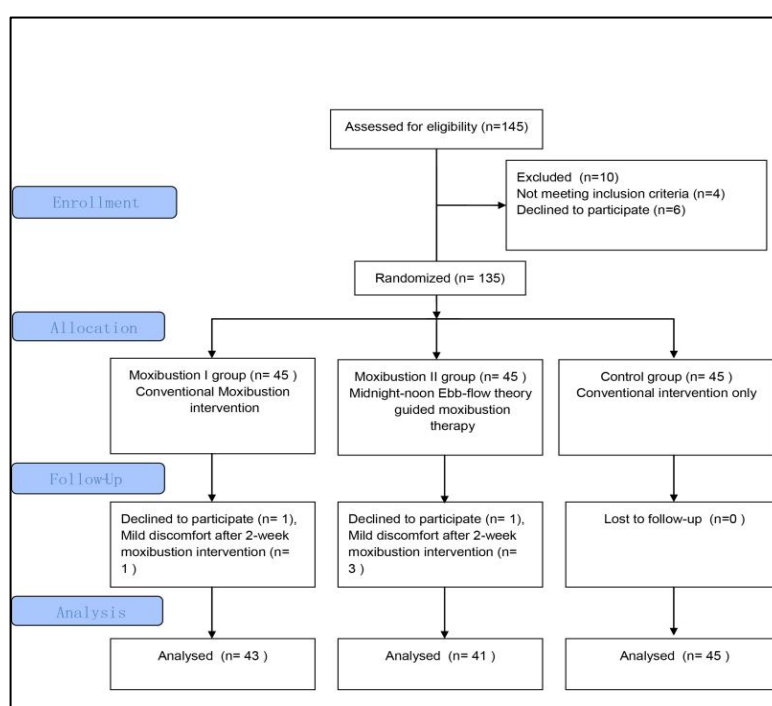


Figure 1 Consolidated Standards of Reporting Trials flow chart

Table 1 Baseline characteristics of study participants

Parameters	Control group (n = 45)	Moxibustion group I (n = 43)	Moxibustion group II (n = 41)	F/ χ^2	P value
Gender, n				0.59	0.75
Female	10	9	6		
Male	35	34	32		
Age (yr)	45.67 $\pm$ 12.01	43.83 $\pm$ 13.13	43.67 $\pm$ 17.25	0.01	0.90
Time from diagnosis (yr)	8.67 $\pm$ 1.03	9 $\pm$ 0.90	8.03 $\pm$ 1.01	0.23	0.80
Marital status, n	43	40	37	0.93	0.63
Employed, n	40	36	35	0.51	0.77
Education level, n				1.83	0.77
Undergraduate studies or above	5	7	8		
High school diploma	22	20	21		
Middle school or below	18	16	12		
Medication, n				7.31	0.12
NSAIDs	40	44	42		
DMARDs	10	13	12		
TNF inhibitors	23	19	20		
BATH scores:					
BASFI (0-100)	30.5 $\pm$ 3.39	31.67 $\pm$ 2.42	29.33 $\pm$ 2.73	0.98	0.40
BASMI (0-10)	4.68 $\pm$ 0.47	5.28 $\pm$ 0.43	5.03 $\pm$ 0.48	2.55	0.11
BASDAI (0-10)	3.15 $\pm$ 0.33	3 $\pm$ 0.65	3.42 $\pm$ 0.49	1.03	0.38
ASQoL (0-18)	11.77 $\pm$ 1.74	12.35 $\pm$ 0.34	12.90 $\pm$ 0.22	1.82	0.20
Laboratory examinations:					
ESR, mm/h	37.5 $\pm$ 1.64	28 $\pm$ 1.41	27.17 $\pm$ 2.48	0.29	0.75
CRP, mg/dL	15.17 $\pm$ 1.47	14.67 $\pm$ 1.63	15.50 $\pm$ 1.52	0.44	0.95
IL-6	6.83 $\pm$ 0.75	6.37 $\pm$ 0.85	6.42 $\pm$ 0.44	0.80	0.47
IL-17	8.85 $\pm$ 0.62	8.62 $\pm$ 0.92	8.15 $\pm$ 0.91	1.12	0.35
TNF- α	13.77 $\pm$ 0.44	14.42 $\pm$ 0.51	13.74 $\pm$ 1.33	1.19	0.33
CD4 ⁺ CD25 ⁺ CD27 low Treg (Treg ratio in the serum %)	39.17 $\pm$ 0.19	39.98 $\pm$ 1.03	39.15 $\pm$ 0.63	1.54	0.25

NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASQoL, ankylosing spondylitis quality of life questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; IL-17, Interleukin-17; TNF- α , tumor necrosis factor- α

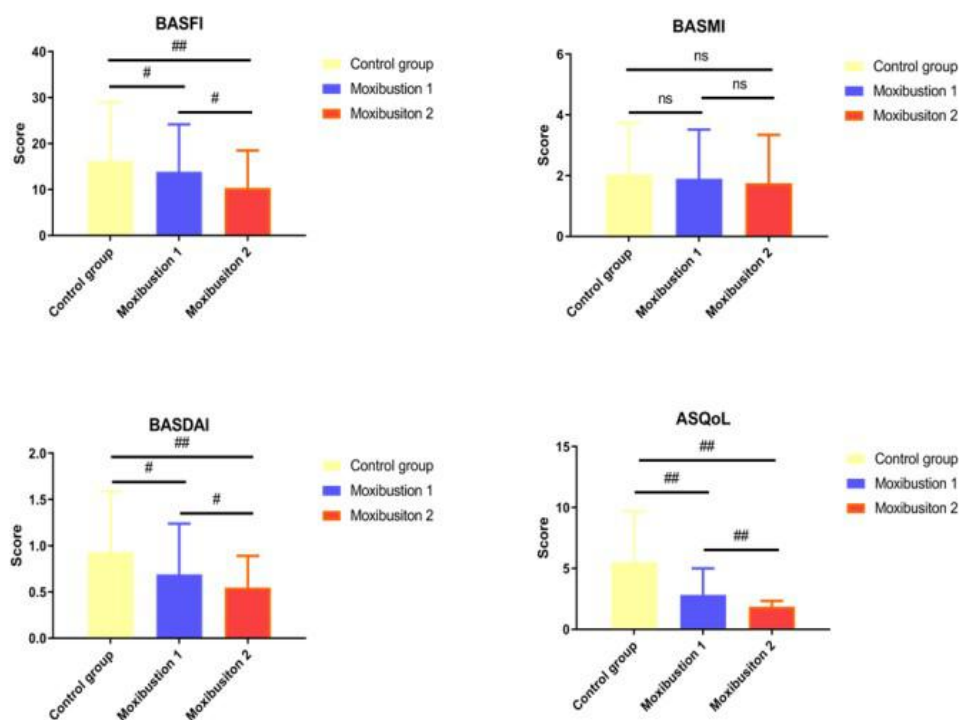


Figure 2 Comparisons of changes in BATH scores and ASQoL scores between groups

Laboratory examinations Compared with the control group, the MNEF-theory based moxibustion group and conventional moxibustion group had a greater improvement from baselines in serum levels of ESR ($F = 18.2$, $P < 0.01$), IL-6 ($F = 12.81$, $P < 0.01$), IL-17 ($F = 70.13$, $P < 0.01$), TNF- α ($F = 55.22$, $P < 0.01$) and the ratio of CD4⁺CD25⁺CD127^{low} ($F = 24.78$, $P < 0.01$) at week 6 (Figure 3). However, no differences were found between the three groups in terms of serum levels of CRP ($F = 0.12$, $P = 0.88$) (Figure 3).

Moreover, the effect of MNEF-theory based moxibustion was shown to be better than conventional moxibustion therapy in the level of ESR (2.67, 95% CI, 0.15 to 5.18; $P = 0.04$) and the ratio of CD4⁺CD25⁺CD127^{low} (-2.83, 95% CI, -4.68 to -0.98; $P < 0.01$). However, with the use of the Tukey multiple comparisons test, compared with the conventional moxibustion therapy alone, MNEF-theory based moxibustion therapy had no statistically significant improvement in the serum levels of IL-6, IL-17, TNF- α ($P > 0.05$).

Safety reports

Only six patients reported mild discomfort after 2-week moxibustion

intervention in this study (Figure 1).

Discussion

AS is a chronic progressive and non-specific inflammatory autoimmune disease mainly involving the sacroiliac joint and spinal axial joint. The main manifestations are inflammatory low back pain, spinal ankylosis, and motor dysfunction. The disease is frequently found in young people aged between 15 and 31. The incidence rate of males and females is 3.4:1. The disease duration of AS is relative long; the disability rate is high. AS seriously affect the quality of life of patients, and bring a great economic burden to their families and the society. At present, the etiology of AS mainly includes genes, autoimmunity, microbial infection, endocrine disorders, and other factors. With the continuous development of the research on AS, some data show that the risk of malignant tumor in patients with AS is as high as 14%. At the same time, the physical, psychological, social, and economic burden also leads to the increased risk of depression in patients with AS. Therefore, AS patients need to seek more effective complementary and alternative medicine.

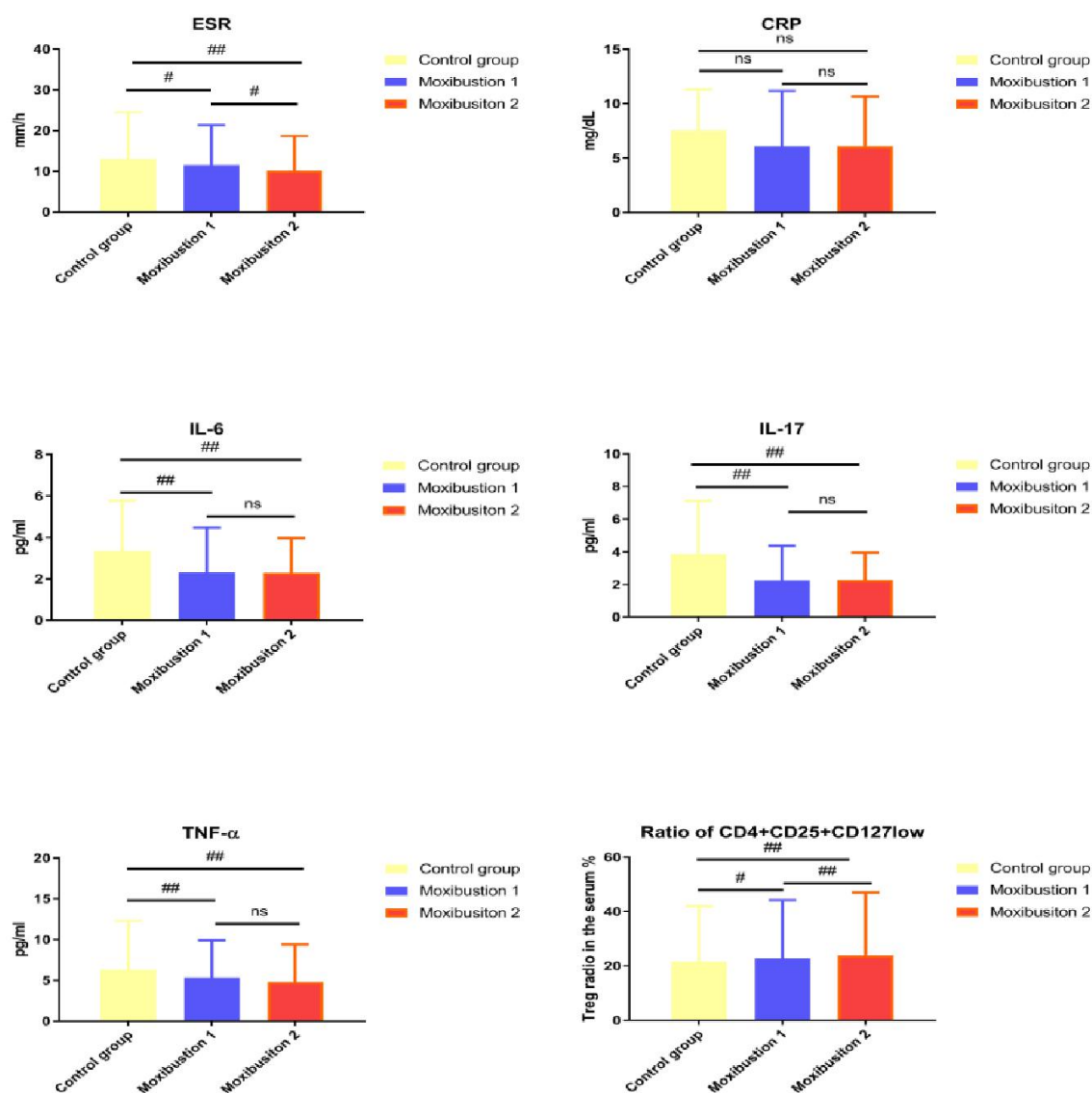


Figure 3 Comparisons of changes in lab examinations between groups

Assessment of physical function and health-related quality of life

Recently, Wang et al. [30] found that the pain VAS score, chest expansion, Schöber test, occipital wall distance, ESR, CRP, IL-6, and TNF- α of 50 patients with AS were significantly improved after 4 weeks of treatment with moxibustion based on oral diclofenac sodium tablets and sulfasalazine tablets. To dispel cold and remove dampness for AS patients. Feng et al. [31] treated 60 patients with AS of kidney deficiency and Du cold syndrome with meloxicam and sulfasalazine plus Du moxibustion for 3 months. It was found that the short-term total effective rate of the observation group was significantly higher than that of the control group. Moreover, after treatment, the scores of visual analogue scale (VAS), finger ground distance, occipital wall distance, lumbar mobility, BASDAI, and BASFI were significantly improved, and the serum levels of ESR, CRP, tumor necrosis factor- α (TNF- α), and interleukin (IL-6) were significantly lower than those in the control group. Parallel to these previous researches, the BASFI score indicated a statistically significant reduction for the moxibustion plus conventional therapy group in the 6th-week measures. In contrast to the positive effects of the BASFI score, there was no statistically significant difference between the two groups in terms of the BASMI index. Consistent with our results, in 2009, Widberg K et al. [32] performed a physical therapy on AS patients. However, there was also no significant difference between the intervention group and the control group in terms of the BASMI scores. To explore the conflict results between groups, in agreement with the previous study [32, 33], the BASMI scale was measured by the professional physicians and the BASFI scale was a patient-reported outcome measurement. The previous study had proved that the health-related quality of life score had a close relationship with the BASFI and the BASDAI scores of AS patients [34]. Thus, moxibustion can improve the physical function of AS patients and ultimately improve the health-related quality of life for AS patients.

Assessment of blood analysis

Cytokines play important roles in the pathogenesis of AS, which not only amplify the effect of the “immune-inflammation” reaction but also stimulate the production of vascular endothelial growth factors. The above pathological reaction may result in vascular infiltration and tissue regeneration in joints, as well as the ossification of AS ligament. TNF- α is mainly produced by activated macrophages and monocytes and is considered to be the master orchestrator of systemic immune-inflammatory response. Mice overexpressing membrane-bound TNF showed typical “bamboo” like changes in the spine and new bone formation at the vertebral angle. IL-6, a cytokine mainly secreted by the monocyte-macrophage, may activate Th cells, maintain the growth and differentiation of B cells, and produce immunoglobulin. Moreover, IL-6 can directly act on T lymphocytes and neutrophils by binding to its membrane surface receptor IL-6R, which may induce persistent chronic inflammation, and result in cartilage metaplasia and calcification, connective tissue proliferation and vertebral fusion. In this inflammatory microenvironment, Th17 cells can recruit neutrophils, macrophages and epithelial cells by secreting IL-17 and releasing other proinflammatory cytokines (such as IL-1 β , IL-6 and TNF- α), which may form continuous positive feedback to result in the inflammatory injury to the ligament of AS. However, MNEF-guided moxibustion therapy can significantly reduce the serum levels of TNF- α , IL-6 and IL-17, which proved that moxibustion can ameliorate the inflammation-induced injury for AS mice. Up-regulating expressions of ESR and CRP played an important role in the pathogenesis of AS [14, 35]. In the present study, although significant improvement in serum levels of ESR was observed, add-on moxibustion interventions did not change the serum levels of CRP in patients with AS. A recent systematic review conducted by Lv et al. [36] also showed favorable effects of acupuncture therapy on serum levels of ESR in AS patients, which was in line with the results of the current study. However, there was no statistically significant difference between the intervention group and the control group in terms of the levels of CRP. More studies and evidence need to further clarify the effectiveness of MNEF-guided moxibustion intervention on

the expression of ESR and CRP for AS patients. Treg is a kind of T cell subset that controls the immune response in vivo. It can inhibit the function of Th cells and antigen-presenting cells through direct contact between cells or secretion of anti-inflammatory cytokines, reduce the secretion of inflammatory cytokines and antibodies, and finally exert an immune effect. The study found that the ratio of CD4⁺CD25⁺ Treg cells in peripheral blood of patients with AS was significantly lower than that of healthy people. Meanwhile, the imbalance in the number and function of Th17 and Treg cells has been proved to be closely related to the disease process of AS. The previous study had found that moxibustion could regulate the immune dysfunction of AS by increasing the serum mRNA expression of Foxp3 and T-bet and the ratio of CD4⁺CD25⁺ Treg and CD4⁺ Th1 cells. Moreover, according to our previous experimental study, moxibustion modulates immune responses and metabolic processes in collagen-induced arthritis (CIA) rat models. In line with the previous studies, in this research, moxibustion exerted a positive effect on improving the ratio of CD4⁺CD25⁺CD127 low in MNEF-theory guided moxibustion intervention programs. Thus, MNEF-theory guided moxibustion intervention might play a critical role in regulating the immune system of AS patients. In this research, only a small proportion of AS patients quit moxibustion intervention. To explore this issue, the moxibustion intervention was supervised by TCM nursing practitioners in the intervention group. Moreover, in our research, no significant adverse events were found in the intervention group except for mild discomfort, which was somewhat in line with the previous study [37, 38]. The high adherence to moxibustion may also contribute to the reduction of inflammatory cytokines in AS patients in the intervention group.

Possible mechanisms of MNEF-theory guided moxibustion for treating AS

From TCM perspective, AS is seen as “Bi syndrome,” which resulted from the cold dampness obstruction in Du meridian. When Xie-pathogenic (cold, damp and coagulation) disturbed the defensive Qi entering into kidney Yang, then pain, stiffness and disability may appear in AS patients. According to MNEF theory, Qi at You time 5:00-7:00 p.m. flowed and poured into the Kidney Meridian. Thus, for AS patients with a clear onset time (5:00-7:00 p.m.), patients in the MNEF-theory guided moxibustion group can obtain better therapeutic effects in terms of BASFI, BASDAI, ASQoL, and inflammatory indicators in this clinical trial.

Shenshu (BL 23) belongs to the foot Taiyang bladder meridian and the back Shu acupuncture point of the kidney, which lines in the second lumbar spine, 1.5 cun next to the posterior midline. SuWen points out that the back Shu acupuncture points can best reflect the rise and fall of the deficiency of the five zang organs; Shenshu is a place for storing the essence. Moxibustion at Shenshu acupuncture points can nourish the kidney yang.

Mingmen (Du 4) acupuncture point is also the gate of life. It belongs to the governor vessel. Mingmen acupuncture point is in the depression under the spinous process of the second lumbar spine, on the posterior midline, the governor's vessel is the sea of Yang vessel. Mingmen acupuncture point is the foundation of Zang Fu organs. It mainly focuses on helping to enhance the Yang and Qi. Yaoyangguan (Du 3) is located in the depression under the spinous process of the 4th lumbar spine on the governor's line. It has the function of nourishing the kidney and strengthening the back and knees.

Conclusions

Overall, MNEF-theory guided moxibustion therapy significantly improved BASDAI, BASFI, ASQoL, reduced the ESR, IL-6, IL-17, TNF- α , and enhanced the ratio of CD4⁺CD25⁺CD127 low for patients with AS.

References

1. Braun J, Sieper J. Ankylosing spondylitis. *Lancet*.

- 2007;369(9570):1379-1390.
[https://doi.org/10.1016/S0140-6736\(07\)60635-7](https://doi.org/10.1016/S0140-6736(07)60635-7)
2. Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromsø, northern Norway. *Ann Rheum Dis*. 1985;44(6):359-367.
<https://doi.org/10.1136/ard.44.6.359>
 3. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford)*. 2014;53(4):650-657.
<https://doi.org/10.1093/rheumatology/ket387>
 4. Liao ZT, Pan YF, Huang JL, et al. An epidemiological survey of low back pain and axial spondyloarthritis in a Chinese Han population. *Scand J Rheumatol*. 2009;38(6):455-459.
<https://doi.org/10.3109/03009740902978085>
 5. Shen BY, Zhang AX, Liu JW, et al. Body image disturbance and quality of life in Chinese patients with ankylosing spondylitis. *Psychol Psychother*. 2014;87(3):324-337.
<https://doi.org/10.1111/papt.12016>
 6. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. *Ann Rheum Dis*. 2001;60(4):353-358.
<https://doi.org/10.1136/ard.60.4.353>
 7. Boonen A, van der Heijde D, Landewe R, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis*. 2002;61(5):429-437.
<https://doi.org/10.1136/ard.61.5.429>
 8. Boonen A, Brinkhuizen T, Landewé R, van der Heijde D, Severens JL. Impact of ankylosing spondylitis on sick leave, presenteeism and unpaid productivity, and estimation of the societal cost. *Ann Rheum Dis*. 2010;69(6):1123-1128.
<https://doi.org/10.1136/ard.2009.116764>
 9. Sieper J, Poddubnyy D. New evidence on the management of spondyloarthritis. *Nat Rev Rheumatol*. 2016;12(5):282-295.
<https://doi.org/10.1038/nrrheum.2016.42>
 10. Dougados M, Behier JM, Jolchine I, et al. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum*. 2001;44(1):180-185.
[https://doi.org/10.1002/1529-0131\(200101\)44:1%3C180::AID-ANR24%3E3.0.CO;2-K](https://doi.org/10.1002/1529-0131(200101)44:1%3C180::AID-ANR24%3E3.0.CO;2-K)
 11. Haibel H, Brandt HC, Song IH, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. *Ann Rheum Dis*. 2007;66(3):419-421.
<https://doi.org/10.1136/ard.2006.054098>
 12. Mansour M, Cheema GS, Naguwa SM, et al. Ankylosing spondylitis: a contemporary perspective on diagnosis and treatment. *Semin Arthritis Rheum*. 2007;36(4):210-223.
<https://doi.org/10.1016/j.semarthrit.2006.08.003>
 13. Chatfield SM, Dharmage SC, Boers A, et al. Complementary and alternative medicines in ankylosing spondylitis: a cross-sectional study. *Clin Rheumatol*. 2009;28(2):213-217.
<https://doi.org/10.1007/s10067-008-1029-3>
 14. Sun ZL, Xu X, Du SZ, Jing X. Moxibustion for treating rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. *Eur J Integr Med*. 2014;6(6):621-630.
<https://doi.org/10.1016/j.eujim.2014.08.002>
 15. Choi TY, Lee MS, Kim JI, Zaslawski C. Moxibustion for the treatment of osteoarthritis: an updated systematic review and meta-analysis. *Maturitas*. 2017;100:33-48.
<https://doi.org/10.1016/j.maturitas.2017.03.314>
 16. Choi TY, Kim TH, Kang JW, Lee MS, Ernst E. Moxibustion for rheumatic conditions: a systematic review and meta-analysis. *Clin Rheumatol*. 2011;30(7):937-945.
<https://doi.org/10.1007/s10067-011-1706-5>
 17. Emanuel EJ. Reconsidering the Declaration of Helsinki. *Lancet*. 2013;381(9877):1532-1533.
[https://doi.org/10.1016/S0140-6736\(13\)60970-8](https://doi.org/10.1016/S0140-6736(13)60970-8)
 18. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.
<https://doi.org/10.7326/0003-4819-158-3-201302050-00583>
 19. Cheng CW, Fu SF, Zhou QH, et al. Extending the CONSORT Statement to moxibustion. *J Integr Med*. 2013;11(1):54-63.
<https://doi.org/10.3736/jintegrmed2013009>
 20. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4):361-368.
<https://doi.org/10.1002/art.1780270401>
 21. Zhang D, Liu W, Yang HJ, Wu YH. [Clinical review of ankylosing spondylitis treated with acupuncture and medicine]. *Chin Acupunct Moxibustion*. 2016;36(8):893-896.
<https://doi.org/10.13703/j.0255-2930.2016.08.032>
 22. Chen J. I - The general diagram of relationship between the whole channels-points and anatomical structures. In: *Anatomical Atlas of Chinese Acupuncture Points*. 2013:CP1-CP2.
<https://doi.org/10.1016/B978-0-08-029784-2.50008-5>
 23. Chen ZL, Pang GS. [Acupuncture assisted by dynamic moxibustion for adult ankylosing spondylitis at early-to-mid stage]. *Chin Acupunct Moxibustion*. 2016;36(11):1157-1160.
<https://doi.org/10.13703/j.0255-2930.2016.11.014>
 24. Xu X, Cao L, Mwandalima CJ, Wang Z, Liu L, Sun ZQ. Protocol for systematic review and meta-analysis: moxibustion for treating ankylosing spondylitis. *Eur J Integr Med*. 2017;12:142-146.
<https://doi.org/10.1016/j.eujim.2017.05.005>
 25. Zhu LL, Zhou JY, Luo L, et al. Comparison of the efficacy between conventional moxibustion and smoke-free moxibustion on knee osteoarthritis: study protocol of a randomized controlled trial. *Trials*. 2017;18(1):188.
<https://doi.org/10.1186/s13063-017-1846-2>
 26. Yang J, Chen J, Lao L, et al. Effectiveness study of moxibustion on pain relief in primary dysmenorrhea: study protocol of a randomized controlled trial. *Evid Based Complement Alternat Med*. 2014;2014:434978.
<https://doi.org/10.1155/2014/434978>
 27. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol*. 1994;21(12):2281-2285.
<https://pubmed.ncbi.nlm.nih.gov/7699629/>
 28. Lin ZM, Gu JR, He PG, et al. Multicenter validation of the value of BASFI and BASDAI in Chinese ankylosing spondylitis and undifferentiated spondyloarthropathy patients. *Rheumatol Int*. 2011;31(2):233-238.
<https://doi.org/10.1007/s00296-009-1313-9>
 29. Zhao LK, Liao ZT, Li CH, et al. Evaluation of quality of life using ASQoL questionnaire in patients with ankylosing spondylitis in a Chinese population. *Rheumatol Int*. 2007;27(7):605-611.
<https://doi.org/10.1007/s00296-006-0267-4>
 30. Wang Q. The influence on bath index of AS patients with deficiency of liver and kidney by using herb cake moxibustion. *J Clin Acupunct Moxibustion*. 2012;28(11):48-50.
<https://doi.org/10.3969/j.issn.1005-0779.2012.11.019>
 31. Feng H, Ma YH, Wang XM. Moxibustion on Governor Vessel for ankylosing spondylitis due to kidney yang deficiency: a clinical controlled study. *J Acupunct Tuina Sci*. 2015;13:361-367.
<https://doi.org/10.1007/s11726-015-0883-1>
 32. Widberg K, Karimi H, Hafstrom I. Self- and manual mobilization improves spine mobility in men with ankylosing spondylitis—a randomized study. *Clin Rehabil*. 2009;23(7):599-608.
<https://doi.org/10.1177/02692155080101748>

33. Kasapoglu Aksoy M, Birtane M, Tastekin N, Ekuklu G. The effectiveness of structured group education on ankylosing spondylitis patients. *J Clin Rheumatol*. 2017;23(3):138-143. <https://doi.org/10.1097/RHU.0000000000000499>
34. Bodur H, Ataman S, Rezvani A, et al. Quality of life and related variables in patients with ankylosing spondylitis. *Qual Life Res*. 2011;20(4):543-549. <https://doi.org/10.1007/s11136-010-9771-9>
35. Li D, Yan B, Chang M, et al. Moxibustion for ankylosing spondylitis: A systematic review and meta-analysis. *Eur J Integr Med*. 2020;35:110-116. <https://doi.org/10.1016/j.eujim.2017.05.005>
36. Lv ZT, Zhou X, Chen AM. [Acupuncture therapy versus disease-modifying antirheumatic drugs for the treatment of ankylosing spondylitis—a meta-analysis]. *Forsch Komplementmed*. 2015;22(6):395-402. <https://doi.org/10.1159/000442733>
37. Furuse N, Shinbara H, Uehara A, et al. A multicenter prospective survey of adverse events associated with acupuncture and moxibustion in Japan. *Med Acupunct*. 2017;29(3):155-162. <https://doi.org/10.1089/acu.2017.1230>
38. Lee J, Yoon SW. Efficacy and safety of moxibustion for relieving pain in patients with metastatic cancer: a pilot, randomized, single-blind, sham-controlled trial. *Integr Cancer Ther*. 2014;13(3):211-216. <https://doi.org/10.1177/1534735413510025>