Clinical trial

Moxibustion therapy in Chinese patients with ankylosing spondylitis: A randomized controlled pilot trial

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ABSTRACT

Introduction: Moxibustion has been widely used in East Asia to manage patients with ankylosing spondylitis (AS). This study aimed to evaluate the short-term effectiveness and safety of moxibustion therapy for treating AS.
Methods: This single-blind randomized controlled pilot study was conducted from August 2018 to January 2019 on 76 AS patients, who were randomly allocated to either a control (n = 32) or an intervention group (n = 30). The control group received conventional intervention alone, while the intervention group received in-patient moxibustion therapy in addition to their conventional intervention for four weeks. Musculoskeletal BATH scores, HRQoL(health-related quality of life), and blood samples were assessed at baseline and at the endpoint-week 6.
Results: Moxibustion significantly improved physical function and decreased disease activity, according to the BASFI (bath ankylosing spondylitis functional index) and BASDAI (bath ankylosing spondylitis disease activity) indexes, respectively ($p < 0.05$), whereas the BASMI (bath ankylosing spondylitis metrology index) index did not reveal significant differences between groups ($p > 0.05$). Additionally, moxibustion produced significant improvement in some domains of the SF-36 (Short form 36 health survey) HRQoL and ASQOL (ankylosing spondylitis quality of life) scale ($p < 0.05$), whereas no effect was observed in CRP (C-reactive protein) serum levels ($p > 0.05$).
Conclusion: Moxibustion in combination with conventional therapies may exhibit beneficial effects for AS patients in the short-term, such as improved physical function and health-related quality of life and decreased disease activity. However, these positive results should be interpreted with caution, as most of the included outcomes were limited to self-assessment tools, and there were no appropriate placebo controls or long-term follow-ups. Further research is needed that would utilize an appropriate moxibustion placebo device and include more objective outcomes, which could evaluate the long-term effectiveness of moxibustion interventions on AS.

1. Introduction

Ankylosing spondylitis AS is a progressive inflammatory disease of unknown origin that affects the axial skeleton and causes enthesitis, and frequently involves extra-skeletal structures such as the bowel, skin, and eyes [1]. The average prevalence of AS has been reported to be 1.0–1.5% in the United States, 0.55% in Germany, 1.1–1.4% in Norway, and 0.2–0.3% in China [2–4]. The main clinical characteristics of AS

consist of inflammatory back pain; alternating buttock pain, chest pain, enthesitis in the heel, synovitis in the lower limbs, peripheral arthritis, fatigue, and other organ manifestations such as Crohn's disease/ulcerative colitis, uveitis, and psoriasis [5]. In addition, AS also affects patients' daily activities, decreases HRQoL, increases sick leave from work, and influences health care resource utilization [6–9].

According to the Assessment of ASAS/EULAR recommendation, NSAIDs (nonsteroidal anti-inflammatory drugs), DMARDs (disease modifying anti-rheumatic drugs), and TNF (tumor necrosis factor) inhibitors are the most important drugs for treating AS [10]. Both selective and non-selective NSAID medication may slow down radiographic progression in AS patients; however, these agents are frequently associated with adverse cardiovascular and renal effects [11]. Traditional DMARDs demonstrate no effect on axial manifestations of AS patients [12], whereas TNF inhibitors (e.g. adalimumab, etanercept, and infliximab) can substantially decrease pain and disease activity and improve physical function for AS patients. Nevertheless, these agents may be too expensive for Chinese AS patients [13].

Thus, more and more AS patients have turned their attention to complementary and alternative medicine (CAM) [14]. Manipulative and manual therapy (MMT), an integral part of CAM, was recommended as a non-pharmacological therapy by the ASAS/EULAR international guidelines in 2010 [15]. To date, there are different styles of MMT for the management of various diseases [16–19], of which moxibustion if one of the most common for the treatment of rheumatic autoimmune diseases in China [20,21]. According to a recent cross-sectional study, moxibustion is considered to be one of the most accepted MMTs for the management of rheumatic conditions in China, besides massage and acupressure [22]. Moreover, in another cross-sectional study, 50% of Korean medical doctors were reported to utilize moxibustion (30–40 min, twice a week) as one of their main methods to treat arthritis patients [23]. According to the Chinese *zang-fu* theory, AS belongs to the *Bi* syndrome. Moxibustion may effectively strengthen the body's ability to restore *Yang* and warm meridians, channel and expel the cold, and promote *Qi* and blood circulation to remove meridian obstructions for AS patients. From the perspective of modern medicine, the effects of moxibustion on immune and bone metabolism regulation as well as its anti-inflammatory and analgesic effects have been investigated previously in arthritic rat models [24–26].

Recently, one published meta-analysis summarized 14 RCTs (randomized controlled trials) (only three clinical trials for AS) involving 1052 inpatients and outpatients to evaluate the efficacy and safety of moxibustion intervention in treating rheumatic conditions [27]. However, previous studies lacked sample size calculation, appropriate randomization and allocation concealment, and essential outcome assessor blinding. Thus, conclusive evidence regarding the efficacy of moxibustion for AS has yet to be established [28]. Therefore, clinical trials following the SPIRIT 2013 and CONSORT statement are essential to verify whether moxibustion is effective for AS [29,30]. Moreover, previous studies only investigated disease activity, physical function, and spinal mobility to assess AS, whereas disease-specific HRQoL or ASQoL indexes were not employed. Furthermore, inclusion of a sham moxibustion device enables double-blinding and thus detects the actual effects of moxibustion. Unfortunately, no completely reliable moxibustion sham devices currently exist. Thus, by employing a similar moxibustion clinical study design, this study performed a pragmatic design and applied conventional intervention as a control [31,32]. Therefore, the aim of this study was to evaluate the short-term effectiveness and safety of moxibustion therapy for the management of AS.

2. Methods

2.1. Ethics statement

The protocol of this research was performed according to the Declaration of Helsinki [33]. The Institutional Review Board of NJUCM

(Nanjing University of Chinese Medicine) approved this clinical trial in March 2018 ([2018] YK006-01), and written informed consents were obtained from every study participant.

2.2. Study design and trial registration

This study was a pilot randomized, assessor-blinded, parallel group, controlled trial. The trial design followed the SPIRIT 2013 [30] (Supplementary A) and extended CONSORT statement to moxibustion [34] and was registered with the Acupuncture-Moxibustion Clinical Trial Registry (AMCTR-IPR-18000206). The study protocol has been published online in the European Journal of Integrative Medicine [35].

2.3. Participants

Patients of the Affiliated Hospital of NJUCM from August 2018 to January 2019 who met the diagnostic criteria for AS [36] were recruited. Inclusion criteria: (1) over 18 years old, (2) undergoing NSAIDs, DMARDs, or TNF antagonists therapy for at least three monnths, (3) able to read and understand at a basic educational level, (4) fully conscious, and (5) refusing to use other CAM therapies during the whole treatment phase. Exclusion criteria: (1) exhibiting other rheumatic diseases (e.g. osteoarthritis, rheumatoid arthritis, Sjogren syndrome, fibromyalgia, systemic lupus erythematosus, etc.), (2) comorbid conditions (f.e. congestive heart failure, uncontrolled hypertension, cancer, etc.), (3) psychiatric disorders or an inability to clearly express their feelings, (4) infectious diseases, and (5) pregnant women.

Participants meeting the inclusion criteria (n = 64) were randomly allocated to the control (n = 32) or intervention group (n = 32). AS patients in the control group received conventional intervention alone, while AS patients in the intervention group received in-patient moxibustion therapy for four weeks in addition to conventional intervention. Musculoskeletal BATH scores, HRQoL, and blood samples were assessed at baseline and at the endpoint-week 6.

2.4. Intervention

2.4.1. Intervention group

The participants in this group received in-patient moxibustion therapy in addition to conventional interventions in the Department of Rheumatology. Moxibustion interventions were given once a day, for 7 days for a total of 4 sessions (4 weeks in total). Outcomes were measured at the endpoint-week 6.

According to the TCM (Traditional Chinese Medicine) theory, kidney deficiency may result in the pathogenesis of AS. Each patient in who suffered from kidney deficiency due to AS was diagnosed by a chief TCM rheumatologist with over 30 years of clinical experience. Based on expert consultations, text books, and systematic review studies, 'Shenshu' (BL23), 'Mingmen' (DU 4), 'Yaoyangguan' (DU 3), and 'ashi' were selected as acupuncture points [37–40]. The acupuncture point locations are described in Supplementary B. After sterilizing the skin surface at selected acupuncture points, patients were instructed to stay in a prone position in a temperature-controlled moxibustion therapy room. A moxa pillar (Nanyang Hanyi Co., Ltd) was lit by a licensed TCM nursing practitioner for approximately 10 s, according to previous studies [41,42]. Then, moxibustion was placed on standard acupuncture points, with the fire head 2–3 cm from the skin. Acupuncture points were treated in the following order: bilateral 'Shenshu', 'Mingmen', 'Yaoyangguan', and additionally two 'ashi' points. In order to prevent burns, once the moxa pillar was burnt out, the TCM nursing practitioner removed the whole moxibustion and replaced it with another one at the same acupuncture point. In total, three moxibustion pillars per acupuncture point were used. Moxibustion at each acupuncture point lasted approximately 6 min and the entire time of moxibustion intervention for each patient lasted approximately 30 min. Moxibustion

intervention details are shown in Supplementary C. The preferred moxa did produce some smoke when burned. Thus, according to safety recommendations for moxa use in previous studies [43,44], a good ventilation and air purification system was integrated into the moxibustion therapy room, which removed toxic substances in moxa smoke. Only one patient reported xerophthalmia, but he completely recovered within a few hours. Thus, the ventilation and air purification systems eliminated any discomfort due to smoke burning from moxa.

Compared with the control group, there is significantly more practitioner-patient interaction in the intervention group. An enhanced doctor-patient relationship may result in better outcomes. Thus, in our research, we tried to establish a "limited" doctor-patient relationship to reduce this bias, according to previously published studies [45,46]. In order to stifle the practitioner-patient relationship during each visit, TCM nursing practitioners were limited to minimal talking (duration < 5 min) to convey "essential" information (introducing themselves, stating that they had reviewed the patient's situation without going into further details, guiding patients to cooperate). Moreover, TCM nursing practitioners were also required to set up neutral expectations for treatment success (f.e. that "treatment success really depended on the patient").

In total, eight TCM nursing practitioners were involved in this study that were registered by the Chinese Nursing Association of the People's Republic of China and completed Chinese Medical University's master education programs as well as three years of rheumatology nursing specialist training.

2.4.2. Control group

AS patients in the control group only received conventional interventions. These included: 1) Medications: rheumatologist-prescribed conventional medications for AS patients according to ASAS/EULAR international guidelines (NSAIDs: Celecoxib, Meloxicam; DMARDs:Sulfasalazine, Methotrexate;: TNF inhibitors Infliximab, Adalimumab; Calcium supplement: D-cal.) [47]. Patients were also encouraged to record any AEs (adverse events) after entry into the clinical trial. 2) Aerobic self-exercise programs: 2018 EULAR International guidelines recommend aerobic exercise as a treatment to improve the range of motion, muscle strength, and well-being of AS patients [48]. Thus, in this study, certain aerobic self-exercise programs were encouraged and provided to patients. In contrast to patients in Western countries, Chinese patients are not attracted and accustomed to yoga and pilates exercise. In addition, walking exercise was not appropriate for AS patients who were admitted to the hospital. Baduanjin Qigong, a relatively simple and low-intensity aerobic exercise, exhibits a beneficial effect on AS patients, according to our previous clinical research [49]. Thus, all AS inpatients in this study attended aerobic Baduanjin Qigong self-exercise programs. During the first week of exercise, the TCM rheumatologist (who had a Qigong exercise coach license) provided step-by-step instructions for AS patients three times a week. During the next three weeks, patients were required to practice Baduanjin Qigong exercise three times per week in the hospital. In order to record their activity and assess their compliance with the recommended program, AS patients were encouraged to record in an exercise training diary the date, type, duration, and intensity of physical activity, using the modified Borg rating of perceived exertion scale [50]. 3) Self-care education programs: During hospitalization, a trained nurse in the Department of Rheumatology worked one-on-one with each individual patient. The nurse provided an assessment regarding the patients' condition and oral instruction following an educational brochure of AS, which included spine structure, physiology, and function, symptoms and prognosis of AS, the risk factors of AS, and side effects of medications. On the 2nd day of admission, interactive consultative communication skills were used by nurses to guide patients to confront and accept AS, to identify problems in self-care needs, resources, and past successful experiences. Finally, trained nurses provided individualized support and counseling according to each patient's

needs (importance of avoiding alcohol and tobacco, methods for relieving back pain, proper diet for AS, the use of medications, weight control issues, etc.). Moreover, nurses also encouraged patients' self-determination to promote their confidence for self-care, as well as provided resources to enhance the ability to solve problems and make decisions. Afterwards, nurses required patients to record a self-care diary and provided weekly feedback [51]. The self-care education program lasted four weeks. All treatments in the control group were also provided to the intervention group.

2.5. Outcomes

There were two visits at the baseline, each at the same time of day. On the initial visit, inclusion and exclusion criteria were reviewed, eligible participants were requested to consent for further screening, and peripheral blood was collected for CRP (C-reactive protein) tests. Participants who met the entry criteria returned on the following day for another visit during which the following was recorded: social, demographic, and clinical characteristics as well as family and individual medical history. The outcome measurement point was chosen six weeks after the end of the treatment and the data collector in this trial was blinded from the group assignment.

The primary outcomes were musculoskeletal BATH scores [52,53]. (1) A Chinese version of the BASFI indexwas utilized to measure the physical function of patients. A numerical rating scale (0–10) ranked each item from 0 ("easy to conduct") to 10 ("impossible to conduct"). (2) A Chinese version of BASMI was utilized to examine the mobility of AS patients. The five dimensions lateral flexion (cm), Schöber test (cm), cervical rotation (cm), intermalleolar distance (cm), and forward flexion (degrees) were assessed by a specialist. Each dimension was assigned a score ranging from 0 to 2, with final sum scores ranging from 0 to 10. (3) A Chinese version of BASDAI was used to measure the disease activity of AS patients. This scale consisted of six items. A numerical rating scale system (0–10) ranked each item from 0 ("none") to 10 ("severe symptoms").

The secondary outcomes included HRQoL and laboratory examinations. (1) HRQoL: A Chinese version of SF-36 was used to assess patient HRQoL with a questionnaire consisting of eight dimensions [54]. The Chinese version of ASQoL (a disease-specific HRQoL tool) contained 18 dimensions. Each dimension assigned a score ranging from 0 to 1, with final sum scores ranging from 0 to 18 [55]. (2) Laboratory tests: serum levels of CRP.

2.6. Randomization and blinding

Using SPSS 22.0 software package (SPSS Inc., Armonk, NY, USA), a blinded statistician generated a random allocation sequence, which was concealed in opaque and sealed envelopes. After each patient agreed to participate in this clinical study and complete baseline measurements, an independent research assistant who was not involved in participant allocation opened the envelopes sequentially. Then, patients were randomly allocated to either the control or intervention group at a 1:1 ratio according to the random allocation sequence.

Although it was impossible to blind the participants and TCM nursing practitioners, statisticians and outcome assessors were blinded [56].

2.7. Statistical methods

The sample size was calculated by NCSS-PASS (Kaysville, Utah, United States) via alpha by 0.05 error, 0.90 power, and −0.65 influence quantity with dual significance levels with 53 patients, according to a previous study [57]. Considering a 20% loss to follow-up, a total of 64 participants were enrolled as eligible study participants.

All statistical analysis was performed using the SPSS 22.0 software package (SPSS Inc., Armonk, NY, USA). In evaluating the demographic
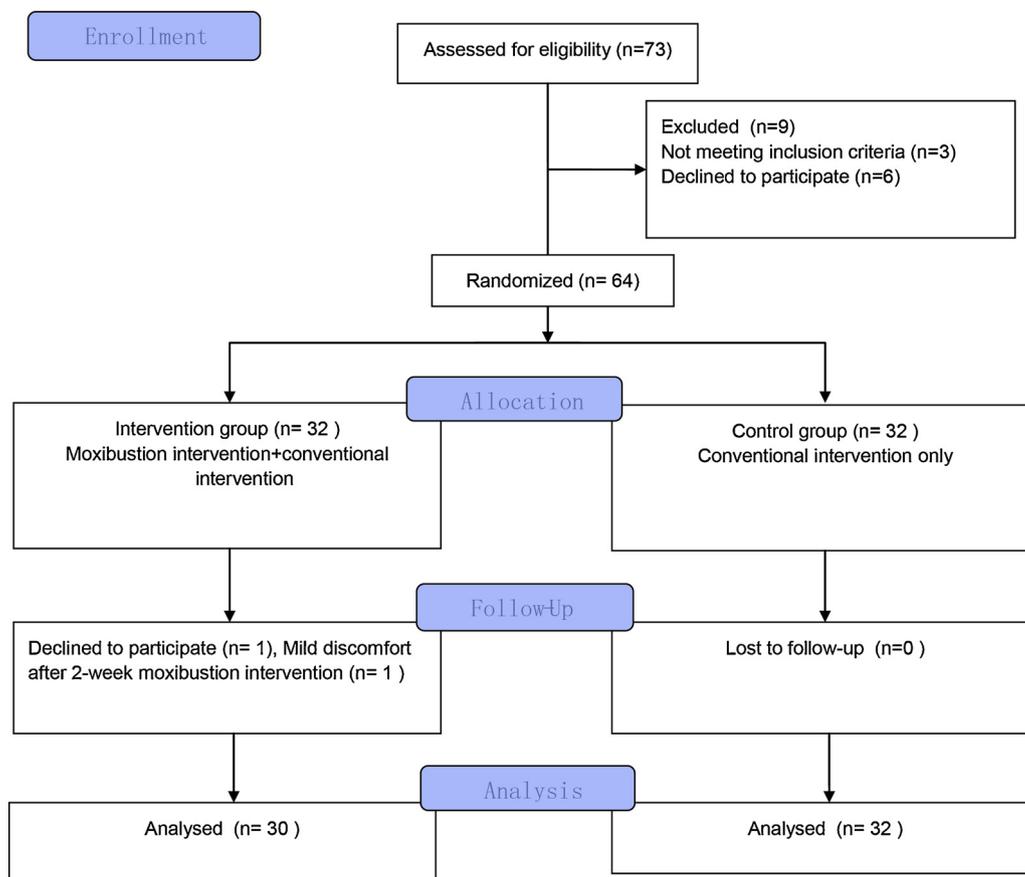
Fig. 1. Consolidated Standards of Reporting Trials flow chart.

data of control and intervention groups, the chi-square test or Fisher's exact test was performed for categorical variables (gender, marital status, employment, education level, medical insurance coverage, HLA-B27 positive, medication usage, etc). After testing for the Shapiro-Wilk test, continuous normally distributed variables were compared by independent *t*-test (age, time from diagnosis, BMI, etc). An independent *t*-test was used for intergroup comparison. Adjusted p value < 0.05 was considered statistically significant for multiple comparisons.

3. Results

3.1. Participant characteristics

From August 2018 to January 2019, a total of 73 patients were screened, 64 patients were recruited, and 62 completed all follow-up assessments. The total dropout rate was 3.2% (n = 2), of which 50% (n = 1) declined further participation. One patient from the intervention group was withdrawn from the study because of mild discomfort, while one patient participated for more than two weeks of moxibustion intervention, but then refused to continue. Fig. 1 depicts the Consolidated Standards of Reporting Trials flow chart for this study.

The baseline patient characteristics (n = 62) are summarized in Table 1. The mean patient age and mean disease durations were 46.53 (SD = 14.96) years and 9.83 (SD = 7.03) years, respectively. Most participants were male (77.42%), had a middle school diploma education level (59.68%), and had health care insurance (98.39%). Most patients were married and had a job. Over 98% of participants were HLA-B27 positive. NSAIDs (79.03%) were the most frequently used in these AS patients. There were no statistically significant differences ($p > 0.05$) between the intervention and control groups regarding gender, age, time from diagnosis, BMI, marital status, occupation, education level, medical insurance coverage, HLA-B27 diagnosis, and

Table 1
Baseline characteristics of study participants.

Parameters	Intervention group (n = 30)	Control group (n = 32)	*P* value
Gender, *n* (%)§			0.46
Female	8 (26.67)	6 (18.75)	
Male	22 (73.33)	26 (81.25)	
Age (yr)†	46.50 ± 16.77	46.55 ± 13.12	0.95
Time from diagnosis (yr)†	10.10 ± 7.50	9.70 ± 6.60	0.82
BMI (Kg/cm²)	23.97 ± 4.12	25.05 ± 4.18	0.31
Marital status, *n* (%)§	24 (80)	27 (84.38)	0.65
Employed, *n* (%)§	23 (76.67)	29 (90.63)	0.14
Education level, *n* (%)§			0.83
Undergraduate studies or above	5 (16.67)	7 (21.88)	
High school diploma	7 (23.33)	6 (18.75)	
Middle school or below	18 (60)	19 (59.37)	
Medical insurance covered, *n* (%)§	28 (93.33)	31 (96.88)	0.52
HLA-B27 positive, *n* (%)§	30 (100)	31 (96.88)	0.33
Medication, *n* (%)§			0.89
NSAIDs	25 (83.33)	24 (75)	
DMARDs	20 (66.67)	23 (71.88)	
TNF inhibitors	5 (16.67)	6 (18.75)	

Note: BMI: Body Mass Index; DMARDs: Disease Modifying Anti-Rheumatic Drugs; TNF inhibitors: Tumor Necrosis Factor;†Independent samples test. §Chi-square test.

Table 2
Comparison of mean scores of key study outcomes at baseline.

Parameters	Intervention group (n = 30)		Control group (n = 32)		P value
	Mean	SD	Mean	SD	
BATH scores [a]:					
BASFI (0˜100)	27.2	13.82	27.14	13.82	0.97
BASMI (0˜10)	5.27	2.27	4.62	3.09	0.4
BASDAI (0˜10)	2.32	0.95	2.42	1.06	0.7
HRQoL [a]:					
ASQoL (0˜18)	5	2.2	4.34	1.91	0.21
SF-36:					
PF	53.67	19.11	60.17	17.29	0.16
RP	33.67	40.92	31.9	41.13	0.87
VT	46.17	14.3	46.38	15.05	0.96
BP	44.48	11.24	45.22	12.62	0.81
GH	57	28.57	52	28.38	0.49
MH	58.67	18.56	60.83	16.88	0.63
SF	47.91	22.04	51.32	16.54	0.49
RE	26.63	16.25	25.98	16.64	0.88
HT	39.17	24.29	39.66	21.67	0.93
Laboratory examinations [a]:					
CRP, mg/dL	13.22	8.7	16.76	8.79	0.11

Note: BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SF-36: short form 36 health survey; PF: physical function; RP: role physical; VT: vitality; BP: bodily pain; GH: general health; MH: mental health; SF: social functioning; RE: role emotional; HT: reported health transition; CRP: C-reactive protein.

medication usage.

3.2. Effects of moxibustion on BATH scores, HRQoL, and CRP

There were no significant differences in BATH scores (BASFI, BASMI, and BASDAI), ASQoL, SF-36, or CRP serum levels between the two groups at baseline (Table 2, all P values > 0.05).

3.2.1. BATH scores
3.2.1.1. BASFI.
The performance of physical function measured by the total BASFI score was significantly different (between-group difference was −4.91 (−9.32 to −0.50); $p = 0.01$) between the two groups (Table 3).

3.2.1.2. BASMI.
Although not statistically significant, there was an improvement in the primary outcome BASMI score in the intervention group compared to the control group (between-group difference was −0.37 (−1.24 to 0.50); $p = 0.40$) (Table 3).

3.2.1.3. BASDAI.
The total BASDAI score showed significant improvement in the intervention group compared with the control

Fig. 2. Changes in ASQOL scores between groups. [#] $p < 0.05$.

group (between-group difference was −0.25 (−0.46 to −0.04); $p = 0.02$)

3.2.2. ASQoL and SF-36
The improvement of ASQoL wasgreater in the intervention group than in the control group with a mean difference of −0.79 (95% CI, −1.39 to −0.19; $p = 0.01$) (Fig. 2). Moreover, significant differences were also noted in the following domains of the SF-36 subscale: physical function (between-group difference was 8.81, 95% CI, 1.57–16.05; $p = 0.02$), role physical (between-group difference was 16.24, 95% CI, 4.95–27.53; $p = 0.03$), bodily pain (between-group difference was 8.47, 95% CI, 1.98–14.96; p = 0.01), social functioning (between-group difference was 9.24, 95% CI, 1.23–17.25; p = 0.02)), and role emotional (between-group difference was 31.31, 95% CI, 12.38–49.88; $p < 0.01$) (Fig. 3).

3.2.3. Serum levels of CRP
Compared with the control group, the intervention group exhibited a decrease in CRP serum levels; however, this decrease was not statistically significant (between-group difference was −1.65 (−4.27 to 0.97); $p = 0.22$) (Table 3).

3.3. Safety reports

No significant AEs were observed during the course of this study. One patient reported xerophthalmia and a tender sensation during the process of moxibustion intervention. Two patients reported mild rubefaction, but they both recovered rapidly within a few hours. Only one patient reported mild discomfort and discontinued moxibustion after two weeks (Fig. 1).

Table 3
BATH scores and laboratory examinations parameters with their comparisons between groups.

Parameters	Intervention group (n = 30)		Control group (n = 32)		Difference (95% CI)	P value
	Mean	SD	Mean	SD		
BATH scores:						
BASFI (0˜100)	11.57	5.51	16.48		−4.91 (−9.32 to −0.50)	0.01
BASMI (0˜10)	2.60	1.54	2.97	1.94	−0.37 (−1.24 to 0.50)	0.40
BASDAI (0˜10)	0.76	0.48	1.02	0.34	−0.25 (−0.46 to −0.04)	0.02
Laboratory examinations:						
CRP, mg/dL	6.22	4.76	7.87	5.74	−1.65 (−4.27 to 0.97)	0.22

Note: BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SF-36: short form 36 health survey; PF: physical function; RP: role physical; VT: vitality; BP: bodily pain; GH: general health; MH: mental health; SF: social functioning; RE: role emotional; HT: reported health transition; CRP: C-reactive protein.
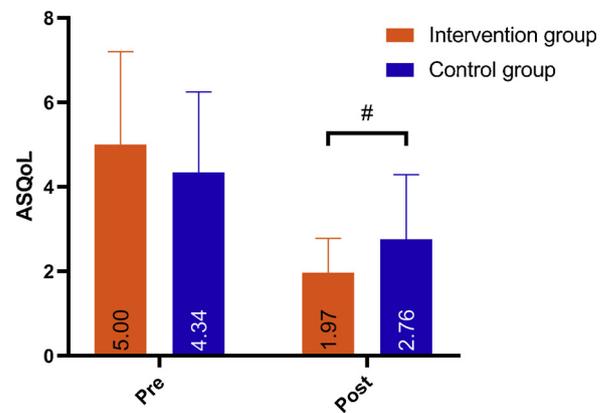Comparison of the BATH scores and laboratory examinations between acupuncture group and waitlist group.
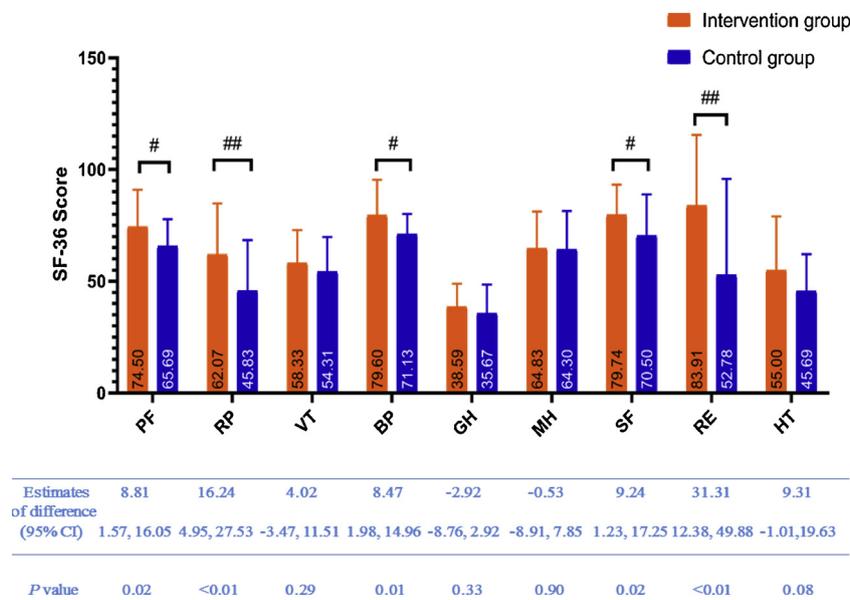
Fig. 3. Changes in SF-36 scores between groups. # $p < 0.05$; ## $p < 0.01$ PH: physical function; RP: role physical; BP: bodily pain; SF: social functioning; RE: role emotional; HT: health transition.

4. Discussion

Overall, the BASFI and BASDAI scores demonstrated that moxibustion significantly improved the physical function and decreased the disease activity compared with the conventional therapy control. However, the BASMI scores did not demonstrate significant differences between groups. Additionally, moxibustion produced significant improvement in some domains of the SF-36 HRQoL and ASQOL scale, compared with the control group.

4.1. Assessment of musculoskeletal BATH score

4.1.1. BASFI score

Studies have demonstrated that subjective patient-reported assessment (BASFI) is a sensitive evaluation of the physical activity of AS patients [58,59]. In contrast to BASFI, BASMI is a professional physician-administered method for assessing spinal mobility in AS patients [53]. However, instead of using the BASMI index, some studies focused only on specific mobility measurements, such as joint range of motion, pain, and morning stiffness [60,61], and have demonstrated that the effects of moxibustion on BASFI and BASMI scores are controversial.

Our results indicate that the BASFI score was significantly lower after moxibustion, compared to the conventional intervention group (11.57 ± 5.51 vs. 16.48 ± 11.39, between-group difference: −4.91 (−9.32 to −0.50); $p = 0.01$. In this study, the combination of moxibustion and conventional interventions improved the physical function of AS patients. The fact that moxibustion is clinically significant for the recovery of physical activity in AS patients is consistent with the findings of previously published studies. A recent clinical trial by Wang et al. [62] demonstrated that a four-week herbcake moxibustion intervention program showed a trend towards BASFI score improvement. Feng et al. [57] investigated the effect of an eight-week acupuncturist-led moxibustion intervention program in 56 AS patients and found statistically significant differences in BASFI scores. Du et al. [63] also found that combined thunder-fire moxibustion at *Jia Ji* acupuncture points, exercise rehabilitation therapy, and sulfasalazine medication therapy was associated with significant improvement in BASFI [63]. Moreover, studies on other manual therapies have also reported positive effects on BASFI scores of AS patients. A recent systematic review revealed favorable effects of acupuncture therapy on BASFI scores in AS patients [61]. Another systematic review also found low to moderate

evidence for the effectiveness of cupping therapy in improving physical function of AS patients [16].

4.1.2. BASMI score

In contrast to the significant BASFI results, we found a noticeable, but not statistically significant, difference in BASMI scores (2.60 ± 1.54 vs. 2.97 ± 1.94, between-group difference: −0.37 (−1.24 to 0.50, $p = 0.40$). We reason that the moxibustion intervention group evaluated their own spinal mobility as more improved than that of the control group, while the statistical evaluations of the two treatment groups did not differ. In contrast, Lam et al. [64] conducted a randomized control trial and found that AS patients who received electroacupuncture (30 min daily, over 6 weeks) had lower BASMI scores [64]. Furthermore, Ning et al. [60] found significant improvements of joint range of motion, pain, and morning stiffness after four weeks of a silver needle nursing program in AS patients [60]. Nevertheless, a RCT on eight-week self- and manual mobilization in AS did not reveal any significant reductions in BASMI scores, consistent with our results [65]. The lack of any moxibustion effects on BASMI scores in our study might be due to the fact that our AS patients at baseline exhibited moderate-to-severe impairments in spinal mobility and relatively longer disease duration. In the studies of Ning et al. [60] and Lam et al. [64], the mean course of disease was five years. However, in our study, AS patients had an average disease duration of more than 9 years. Moreover, some AS patients in our study exhibited high radiological indexes, a waist with ankylosis, and even severe contracture in the spine. Thus, moxibustion intervention may be too gentle to induce changes in the spinal joint range of motion (occipital-wall distance, chest expansion, finger-ground distance of the spine joints, etc.). Furthermore, our study was performed on AS inpatients, and usually the number of AS patients able to participate in an over-four-week in-patient moxibustion intervention program is very limited in China. Previously, a systematic review by Lv et al. [61] summarized six RCTs involving 541 inpatients and outpatients to examine the effects of over eight weeks of acupuncture on AS patients. The results indicated that a combination of acupuncture and DMARDs could further improve BASMI scores compared to DMARD treatment alone. Thus, the superiority of moxibustion in improving BASMI might be present after longer treatment durations.

Several factors may explain the discrepancy between the effects of moxibustion on BASFI and BASMI scores in AS patients. On the one

hand, unlike BASMI, BASFI can only assess simple physical activities (climbing steps, getting up from a chair, dressing, etc.). Thus, BASFI only detects changes in lighter physical tasks and does not assess more intense physical activities. On the other hand, BASFI is a subjective patient-reported index, which is influenced by the level of general education of AS patients [66]. Previous studies have demonstrated that AS patients who had completed their college education may provide a more precise and clear self-assessment [67]. However, in our study, the number of AS patients who completed their college education were limited. Thus, BASFI scoring may adjust over time due to newly gained knowledge and information of AS patients.

Overall, in agreement with previous studies [65,68], the discrepancy between the effects of moxibustion on BASFI and BASMI of AS patients confirms the limited relationship between measurements of physical capacity assessed by a professional physician vs. the patient. Thus it is important to include both BASFI and BASMI when evaluating AS patients.

4.1.3. BASDAI score

BASDAI is an important patient-reported disease activity scale that captures the main AS symptoms (pain, fatigue, morning stiffness, etc.) [69]. Previous research has revealed that moxibustion reduces pain, fatigue, and morning stiffness and can be considered a supplement for standard DMARD therapies for rheumatoid arthritis patients [20]. In this study, we did not specifically focus only on pain, fatigue, and morning stiffness, but these components were still the main parts of the BASDAI index that we assessed. Thus, it could be expected that moxibustion may have a positive effect on BASDAI scores. Chen et al. [38] and Qin et al. [70] demonstrated that four weeks of moxibustion exhibited a trend towards an improved BASDAI score. We confirmed this in our study in which the BASDAI score was significantly reduced in the moxibustion group ($P < 0.05$) compared to the conventional intervention alone (0.76 ± 0.48 vs. 1.02 ± 0.34, between-group difference: -0.25 (-0.46 to -0.04); $p = 0.02$). These results suggest that moxibustion therapy is clinically significant in reducing the disease activity of AS.

In addition, our study also confirms earlier suggestions that there is no linear relationship between disease activity and physician-administered physical function of AS [70]. Additional important environmental and personal components can also influence physical impairments in AS [69,71]. Thus, there is a conflict between the results of BASDAI and BASMI scores.

4.2. Assessment of HRQoL

HRQoL is an important factor affecting the success of disease management in AS [72]. In this study, the generic SF-36 questionnaire and the disease-specific ASQoL questionnaire were used to evaluate AS patients' self-rated HRQoL. So far, only a few clinical trials have evaluated the effectiveness of moxibustion on HRQoL of AS patients [73,74]. Feng et al. [73] showed that physical functioning, bodily pain, and social functioning along with the total SF-36 QoL of AS patients significantly improved after moxibustion. Li et al. [74] indicated that SF-36 QoL dimensions (except for health transition and mental health) were significantly improved in AS patients after four weeks of moxibustion. Our results are partly consistent with that of previous studies that found that moxibustion may have a beneficial effect on a range of SF-36 subscale outcomes (physical function: 74.5 ± 16.46 vs. 65.69 ± 12.13, between-group difference: 8.81 (1.57–16.05), $p = 0.02$; role physical: 62.07 ± 22.74 vs. 45.83 ± 22.6, between-group difference: 16.24 (4.95–27.53), $p = 0.03$; bodily pain: 79.6 ± 15.89 vs. 71.13 ± 9.02, between-group difference: 8.47, (1.98–14.96), $p = 0.01$; social functioning: 79.74 ± 13.53 vs. 70.5 ± 18.43, between-group difference: 9.24, (1.23–17.25), $p = 0.02$, and role emotional: 83.91 ± 31.65 vs. 52.78 ± 43.13, between-group difference: 31.31 (12.38–49.88), $p < 0.01$). Since we could not find

any study that used ASQoL for the evaluation of moxibustion or acupuncture on HRQoL of AS patients, we cannot compare our results with those of others. According to a recent cross-sectional study by Bodur et al. [75], HRQoL (as measured by both SF-36 and ASQoL) was strongly correlated with pain, fatigue, and morning stiffness of AS patients. Thus, the positive effects of moxibustion on reducing pain, fatigue, and morning stiffness could further improve the QoL of AS patients. In the light of these findings, our study suggests that moxibustion therapy is clinically significant in improving HRQoL of AS patients.

4.3. Assessment of blood analysis

Increased serum levels of CRP are important pathogenic mediators in AS patients. Previously, several studies have demonstrated that moxibustion can exert a beneficial effect on reducing the disease activity and systemic inflammation in rheumatic disorders [20,58]. Compared to conventional intervention alone, the CRP serum levels were slightly reduced after moxibustion (6.22 ± 4.76 vs. 7.87 ± 5.74, between-group difference: -1.65 (-4.27 to 0.97); $p = 0.22$), but no statistically significant difference was detected between the two groups. In agreement with our report, a recent systematic review by Lv et al. [61] also demonstrated no significant difference in CRP serum levels between DMARD and acupuncture therapy groups. The results of our study and Zheng's study showed that the effects of acupuncture and moxibustion therapy on CRP serum levels are still controversial. Therefore, in order to obtain more evidence on the effectiveness of moxibustion on inflammatory processes in AS patients, moxibustion-targeted inflammatory biomarkers should be further explored.

4.4. The lasting effects of moxibustion

The lasting effects of moxibustion are one of the most importants and have been demonstrated by clinical trials [76,77]. Zhang et al. [76] demonstrated that both real and sham acupuncture reduce chronic knee pain, but that the effect of real acupuncture was significantly superior to sham acupuncture. In addition, three of thirteen RCTs found that the differences were still significant at the follow-up period. Moreover, a systematic review by Zhu et al. [77] summarized 13 RCTs involving 1723 patients that examined the effect of acupuncture on pain and physical function in patients with cervical spondylosis and demonstrated that acupuncture could further reduce pain and improve physical activity, compared to the usual care. In addition, follow-up observations indicated that acupuncture exhibited more stable and lasting effects. Accordingly, our results also indicate continuous and significant improvements in pain, physical function, and quality of life at the six-week follow-up after moxibustion intervention. *Deqi* sensation might be key for achieving lasting effects following moxibustion [78]. Patients experiencing acupuncture-moxibustion stimulations often report multidimensional sensations such as pressure, numbness, soreness, heaviness, warmth, and dull pain. The classic TCM literature *Inner Canon of the Yellow Emperor* once recorded that "the achievement of acupuncture-moxibustion long-lasting effects depends on the Qi arrival". Moreover, some pre-clinical studies have also demonstrated that *Deqi* was a necessary component of lasting analgesic effects [79,80]. Functional magnetic resonance imaging studies further revealed that the effect of acupuncture with *Deqi* still affected brain activity and the nerve response pattern for a period of time after the cessation of acupuncture [81].

4.5. Compliance and placebo moxibustion

Adherence rates of AS patients in our study were very high and only two patients withdrew from the intervention group. Probable AEs related to moxibustion such as local skin irritation, tenderness, and residual pain at acupuncture points were all commonly reported in a previous systematic review [20]. Whereas patients enrolled in this

study reported no serious moxibustion-related AEs, except for mild discomfort, consistent with a previous report that moxibustion therapies do not cause serious AEs when used on appropriate recipients [82]. Therefore, moxibustion may be considered a relatively safe intervention. In future trials, larger sample populations should be assessed for any moxibustion-associated AEs.

Inclusion of placebo moxibustion that is comparable to the actual effects of moxibustion may be crucial for clinical studies. One sham moxibustion device has been proposed for clinical trials that may achieve patient blinding [83]. Unfortunately, most participants are able to identify the type of moxibustion intervention received, because inappropriate sham moxibustion stimulation at acupuncture points can be easily identified [84]. No completely reliable moxibustion sham method currently exists and thus we did not include sham moxibustion in our study at this time.

4.6. Possible mechanisms of moxibustion for treating AS

One of the possible mechanisms of moxibustion in treating AS is the thermal stimulation effect, which is achieved by stimulating sensory receptors of acupuncture points on the skin. When moxibustion stimulation activates these sensory receptors, the signal can lead to vasodilatation around the acupuncture points and increase peripheral arterial blood flow [85,86]. Moreover, the thermal effect of moxibustion can also be obtained via inducing heat shock proteins (HSPs) in local tissues. As endogenous protective molecules, HSPs may be regulated by moxibustion stimulation and can activate the mitochondrial signal transduction pathway to prohibit cell apoptosis and protect local tissue [87]. Another possible hypothesis is the pharmacological or medicinal effect of the moxa. Moxa is a Compositae Artemisia perennial herb, which includes more than 60 components. After moxibustion combustion, the active ingredients of moxa (Moxi-tar) are increased. Moxi-tar-like substances including tricosariol thujone, and nonacosane have been demonstrated to exert actions such as clearing free radicals, lipid peroxidation, protecting neurons, and relieving colitis [88,89]. Additionally, in a recent CIA (Collagen-induced arthritis) rat model study, moxibustion modulated immune responses and metabolic processes in arthritis. Moreover, inositol 1,4,5-triphosphate receptor and periodxiredoxin I may be potential moxibustion-related targets for arthritis [24]. Furthermore, it was reported that moxibustion could produce analgesic effects through the deregulation of interleukin-1, prostaglandin-E$_2$, and nitric oxide levels after stimulating acupuncture points in CIA rat models [90,91]. Such research indicates mechanisms of moxibustion that might also play a role in alleviating AS symptoms.

4.7. Limitations

This study has several limitations. First, due to the nature of moxibustion intervention, this study was unable to blind moxibustion practitioners and participants. Second, similar to acupuncture therapy, AS participants have high expectations and beliefs regarding moxibustion effectiveness. Thus, we cannot avoid non-specific effects of moxibustion. Third, physical function of AS was evaluated only via patient-reported BASFI and physician-reported BASMI. In the future, radiographic measurements of AS, possibly using X-ray and MRI, must be used in order to enhance the validity of our current results. Fourth, all AS patients received only in-patient routine moxibustion intervention. In the future, alternative study locations such as in the community or out-patient clinics should be selected in order to enhance the representativeness of the study population. Fifth, much effort went to the intervention group. It would be interesting to know whether a long-term moxibustion effect was produced with such intense effort. However, a previous study has revealed that Chinese patients exhibit poor medical adherence in the field of rheumatology during long-term follow-up periods [92]. Moreover, one study reported that only 13 of 32 participants completed all ten acupuncture treatments, suggesting that

acupuncture attendance can be poor [93]. We only performed short-term in-patient moxibustion therapy for AS patients. In the future, our research team will further examine the long-term effects of moxibustion on AS with the help of funding support and community hospital co-operation. Sixth, besides the quantitative design of this study, a qualitative study to assess the AS patient experience of moxibustion is still warranted in the future. Seventh, although a 'limited' doctor-patient relationship and neutral expectations for treatment success were established in this clinical trial, we still could not completely avoid the affective social component in this trial. For example, touch itself has positive effects on a patient's experience of pain and affective state. However, it is impossible for TCM nursing practitioners to perform moxibustion interventions without touching the patient.

5. Conclusion

Short-term moxibustion in combination with conventional therapies might improve physical function and health-related quality of life as well as decrease the disease activity of AS patients. However, these positive results should be interpreted with caution, as most of the included outcomes were limited to self-assessment tools, and the appropriate placebo control and long-term follow-up were lacking. Further research is needed to elucidate the long-term effectiveness of moxibustion interventions, to design an appropriate moxibustion placebo device, and to include more objective outcomes with which we can measure the effectiveness of moxibustion interventions on AS.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2019.100952.

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