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Protocol

Moxibustion intervention for patients with ankylosing spondylitis: A study Protocol for a pilot randomized controlled trial

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ABSTRACT

Introduction: Moxibustion is described as a technique that applies heat which is generated by burning herbal preparations containing Artemisia vulgaris to stimulate acupuncture points. The aim of this study is to assess the efficacy and safety of moxibustion treatment for AS. In the future, a larger RCT will be conducted based on preliminary data from this study.

Methods: This research is a protocol for an open, assessor- and analyst-blinded, randomized clinical trial with two parallel groups. Participants who meet the modified New York criteria for AS will be randomly allocated to the intervention group or the control group with a 1:1 allocation ratio. The intervention group will receive moxibustion intervention for 3 weeks and follow-up for 6 weeks. The control group will not receive moxibustion intervention and will be followed for 6 weeks. Conventional interventions will be allowed for both groups. Primary outcome measures are BASFI, BASDAI, and BASMI. Secondary outcome measures are SF-36, EQ-5D, ASQoL and serum levels of ESR and CRP.

Ethics and dissemination: This protocol has been approved by the Institutional Review Board (IRB) of the Clinical Research Centre (Affiliated Hospital of Nanjing University of Chinese Medicine, IRB No. [2018] YK006-01). In addition, results of this preliminary study will be disseminated through peer-reviewed publications.

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown etiology that mainly affects the axial skeleton and sacroiliac joints [1]. It can be a pathological process characterized by sacroiliitis, synovitis, enthesitis, and bone fusion in spinal joints [2]. Recent data shows that the prevalence of Chinese AS patients aged below 30 years is approximately 0.24% and the disability rate may reach about 65% [3,4]. Limitations in spinal mobility and inflammatory back pain (IBP) are the main biomechanical problems in AS patients [5]. In addition, it can reduce patients' health-related quality of life (HRQoL), decrease patients' psychological health, influence patients' social interactions and sexual activity, and have an important economic impact for the whole society [6,7].

Abbreviations: AS, ankylosing spondylitis; ASQoL, ankylosing spondylitis quality of life; BASFI, bath ankylosing spondylitis functional index; BASDAI, bath ankylosing spondylitis disease activity index; BASM, bath ankylosing spondylitis metrology index; CAM, complementary and alternative; CRP, C-reactive protein; CRF, case report form; DMARDs, disease modifying anti-rheumatic drugs; EQ-5D, EuroQol-5 dimension; ESR, erythrocyte sedimentation rate; ECG, electrocardiogram; HRQoL, health-related quality of life; IBP, inflammatory back pain; IRB, Institutional Review Board; IL -6, interleukin (IL)-6; ITT, Intention-to-treat; NSAIDs, non-steroidal anti-inflammatory drugs; MMT, manual and manipulative therapy; RCT, randomized controlled trial; ROM, range of motion; PI, principal investigator; TCM, traditional and Chinese medicine; TNF, tumor necrosis factor); VAS, visual analogue scale

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Assessment of Spondylo Arthritis international Society/European League Against Rheumatism emphasized that the goal of AS treatment should focus on preventing malfunction and working disability, reducing stiffness and pain, maintaining posture, and promoting psychosocial health [8]. To date, the common pharmacological agents in the clinical practice included non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and TNF antagonists [9]. NSAIDs are the standard first-line treatment modalities for AS [10]. However, this agent is frequently associated with gastrointestinal intolerability and cardiovascular risk increasing [11]. Methotrexate or slfasalazine, the most common DMARDs, might have a beneficial effect on AS patients with peripheral arthritis, but not axial manifestations [12]. Four FDA approved TNF antagonists (adalimumab, etanercept, golimumab and infliximab) have been licensed to prevent the development of syndesmophyte formation and control disease activity in severe AS patients [13]. However, the cost of these most impressive and novel biological agents may limit their usage for AS patients and their families in rural districts [14].

Given these limitations, Traditional and Chinese Medicine (TCM) therapies might be an effective complement to pharmacological agents in AS management [15]. Moxibustion is an important component of TCM that has been considerate as a valuable treatment modality for many rheumatic diseases in China [16,17]. A recent cross-sectional research showed that moxibustion was one of the most widely used manual and manipulative therapy (MMT) for the treatment of rheumatic disorders in mainland China next only to acupuncture and Chinese Tuina [18]. Moreover, roughly 50% of Korean complementary and alternative (CAM) practitioners have utilized this skill for the management of rheumatic diseases, and moxibustion is one of the most popular CAM techniques among arthritis patients in Korea [19]. Furthermore, a bibliometric analysis in China also showed that moxibustion intervention has been widely applied in various kinds of rheumatic disorders, including AS [20]. From the perspective of TCM, AS is typically diagnosed as *Cold Damp Bi syndrome*. Historically, *Huangdi's Classic on Medicine* says: “moxibustion may have a magic treatment effect that acupuncture may not achieve.” Thus, the use of moxibustion is indicated in the treatment of *Cold Damp Bi syndrome* [21]. From the perspective of modern medicine, Moxibustion may reduce the serum levels of tumor necrosis factor (TNF), interleukin (IL)-6, and interleukin (IL)-1 and involve in mediating metabolic reactions and immune process and in an arthritis rat model [22,23].

Recently, one published meta-analysis evaluated moxibustion intervention for rheumatic conditions and included 3 clinical trials for AS (a total of 14 clinical trials) [24]. However, the previous results do not provide convincing evidence to test the efficacy and safety of moxibustion for AS. This may be because of lack of strict control of randomization and allocation concealment, inappropriate outcome assessor and data analysts blinding, poor reporting of adverse events and missing information about the sample size calculation [25].

Thus, high-quality research based on the SPIRIT 2013 and Extending the CONSORT Statement to moxibustion are essential to decide whether moxibustion is effective for AS [26,27]. Moreover, even if sham moxibustion methods have been developed, some discrepancies continue to exist in terms of their reliability [28,29]. Thus, in order to test the clinical effectiveness of moxibustion intervention in the real word, a pragmatic design using a conventional intervention group may be more appropriate in this research [30]. Moreover, the previous clinical trials only employed TCM assessment outcomes; other important international outcomes such as Ankylosing Spondylitis Quality of Life (ASQoL), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) were not involved in the research.

For these reasons, this study will perform a pragmatic randomized clinical trial to assess the efficacy and safety of moxibustion for AS. In the future, a large-scale clinical trial will be conducted based on preliminary results and evidence from this study.

2. Methods

2.1. Aim

The aim of this study is to assess the efficacy and safety of moxibustion treatment for AS.

2.2. Study design

This research is a protocol for an open, assessor- and analyst-blinded, randomized clinical trial with two parallel groups. The protocol will be conducted according to Extending CONSORT statement for moxibustion [26] and SPIRIT 2013 (Supplementary material 1) [27]. This trial will be carried out at a single TCM clinical and research center (Affiliated Hospital of Nanjing University of Chinese Medicine) between 30 August 2018 and 30 December 2019.

After a recruitment period, qualified participants who meet the definitive diagnosis criteria for AS [31] will be randomly allocated to the control group (conventional intervention alone) or the intervention group (moxibustion intervention + conventional intervention) with a 1:1 allocation ratio. Next, all included participants will perform a three week intervention (moxibustion intervention will be conducted three times per week) and six week follow-up period. In total, three key time points (baseline, primary endpoint-week 4 and follow-up point-week 6) will be scheduled for each patient. Results of this study will be analyzed by professional statisticians blinded to the group allocation. This study design is summarized in Fig. 1 and the schedule for this study design is shown in Table 1.

This protocol has been approved by the Institutional Review Board (IRB) of Affiliated Hospital of Nanjing University of Chinese Medicine in March 2018 ([2018] YK006-01). Before the start of collecting information at the first visit, research team members should obtain written consents from each participant. This protocol has also been registered with the Acupuncture-Moxibustion Clinical Trial Registry (AMCTR-IPR-18000206), a secondary register platform affiliated to the Acupuncture Clinical Trial Registration Center site and WHO International Clinical Trials Register Platform (ICTRP)

2.3. Recruitment strategies

Participants will be recruited from the Departments of Rheumatology, Affiliated Hospital of Nanjing University of Chinese Medicine. Moreover, colorful recruitment posters will be handed out in three local communities (Gu Lou community, Xuan Wu community, Xi Xia community). Furthermore, recruitment information will be posted in hospital’s newsletters and through the website.

2.4. Types of participants

2.4.1. Inclusion criteria

Inclusion criteria will be as follows:

- Aged over 18 years
- Fulfilling the definitive diagnosis criteria for AS [31] and GPCRND (guiding principles of clinical research on new drugs) symptom differentiation.
- Disease lasting for over 6 months
- NSAIDs used for more than 4 weeks in a stable situation
- DMARDs (methotrexate, sulfasalazine) or TNF antagonists (adalimumab, etanercept, golimumab and infliximab) use, based on on stable dosages for at least 3 months
- Agreed to not use other TCM therapies (acupuncture, cupping, or herbal medicine) during the whole treatment phase
- Able to speak Chinese

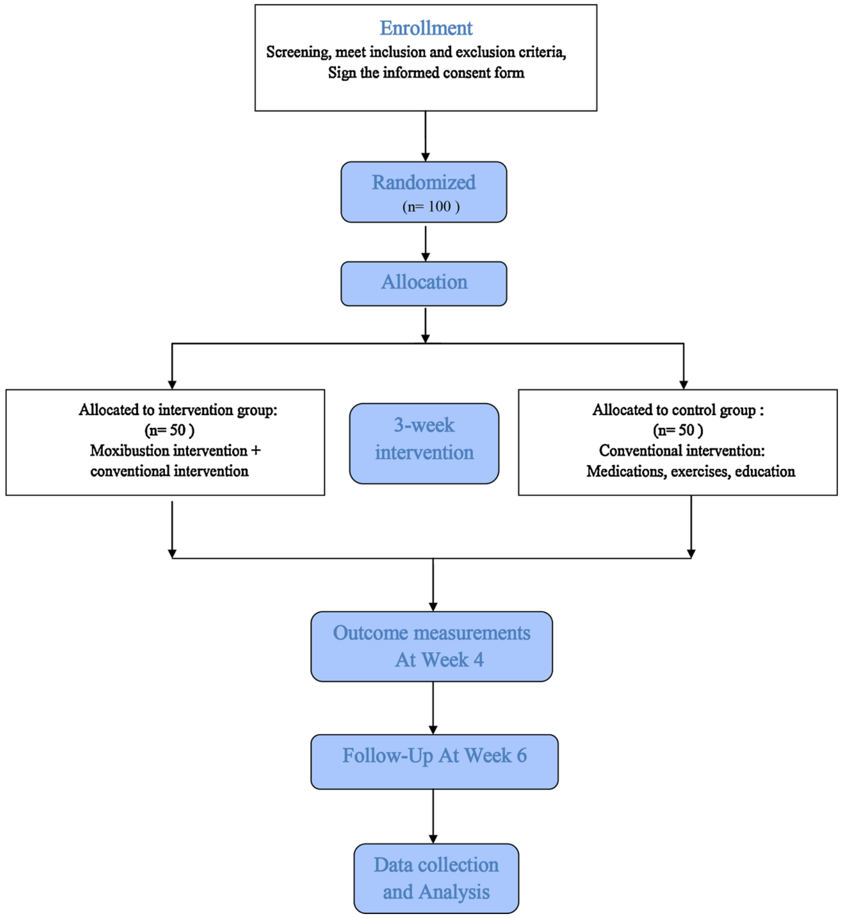

Fig. 1. Flow of the study.

- Able to provide informed consent

2.4.2. *Exclusion criteria*

Exclusion criteria will be as follows:

- Presence of other rheumatic diseases: Systemic lupus erythematosus, osteoarthritis, rheumatoid arthritis, fibromyalgia, Sjogren syndrome,etc.
- A history of heart failure, malignancies, uncontrolled hypertension, chronic obstructive pulmonary disease, lymphoma, neurological and gastrointestinal disorders, haemorrhagic disorders
- Infectious diseases
- A diagnosis of mental disorder
- Pregnant and lactating women
- Previous poor compliance
- Alcohol or drug addiction
- Not suitable for moxibustion: TCM pattern differentiation of *Heat Bi*, moxibustion syncope, unwilling to be treated with moxibustion, etc.

2.4.3. *Discontinuation criteria*

Criteria for discontinuations are defined as follows:

- Serious adverse events
- Participants with severe diseases not found in the screening test
- Participants' request for dropout at any time for any reason
- Significant violation of the clinical trial protocol
- Administration of medicine without the permission from researchers

2.5. *Randomization and allocation concealment*

The Clinical Trial Center (Affiliated Hospital of Nanjing University of Chinese Medicine) will be responsible for the enrollment of eligible participants, the random allocation sequence generation, and randomly assignment of participants to different intervention groups. An independent statistician who is not involved in this study will generate random numbers lists with the help of SPSS statistical package programme (V.22.0). When a randomized table is created, this random allocation sequence will be concealed in opaque and sealed envelopes. After the each participant has completed baseline assessments during the screening period, the envelopes will be opened sequentially in front of the participants by an independent researcher who is blinded in respect of participant allocation and treatments. Then, according to the random allocation sequence, participants will be allocated to either the control group (conventional intervention alone) or the intervention group (moxibustion intervention + conventional intervention). In this study, due to the nature of moxibustion intervention, participants will know which group they will be assigned to However, statisticians and outcome assessors and will be blinded to the participant allocation and treatments [32].

2.6. *Blinding*

In moxibustion intervention research, it is not feasible to conduct double blinding of the moxibustion practitioners and participants. However, to reduce the possible bias of this trial, statisticians and outcome assessors will be blinded to group allocations and interventions during the process of the clinical trial. Moreover, to prevent accidental un-blinding, the moxibustion practitioners, the outcome

Table 1
Clinical Trial Schedule.

Trial Schedule	Period	S					T					F
	Visit	1	2	3	4	5	6	7	8	9	10	11	12
	Week		1	1	1	2	2	2	3	3	3	4	6
Enrollment													
Informed Consent	√												
Sociodemographic Characteristics	√												
Disease, Family and Medical History	√												
Inclusion/Exclusion Criteria	√												
Change in Medical History		←											→
Comorbidities	←												→
Randomization		√											
Intervention													
Moxibustion Intervention		←									→		
Outcome Measurements													
BASDAI		√										√	√
BASFI		√										√	√
BASMI		√										√	√
ASQOL		√										√	√
EQ-5D		√										√	√
SF-36		√										√	√
ESR, CRP	√											√	
Safety Evaluation													
AEs		←											→
Vital Signs	←												→
Dropout or Withdrawals			←										→
Blood Test	√											√	
ECG	√												

AEs: Adverse Events; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-relactive protein; EQ-5D: EuroQol-5 dimensions; ECG: Electrocardiogram; ESR : Erythrocyte Sedimentation Rate; F: Follow-up Period; SF-36: The Short-Form 36v2 Health Survey; S: Screening Period; T: Treatment Period.

Table 2
Details of acupuncture points in moxibustion treatment group.

Acupuncture poins	Location	TCM theory
Shenshu (BL 23)	On the lower back, below the spinous process of the second lumbar vertebra (L2), 1.5cun lateral to the posterior midline	The main cause of AS in TCM is kidney deficiency. Moxibustion at Shenshu can nourish the kidney, strength the lumbar vertebrae.
Mingmen (DU 4)	On the lower back, on the posterior midline, in depression below the spinous process of the second lumber vertebra	Cold-damp coagulation in the Du meridian may result in AS. Mingmen is at the Du meridian, which can warm the kidney and expel cold and strengthen bones.
Yaoyangguan (DU 3)	On the lower back, on the posterior midline, in depression below the spinous process of the fourth lumber vertebra	Cold-damp coagulation in the Du meridian may result in AS. Mingmen is at the Du meridian, which can warm the kidney and expel cold and strengthen bones.

assessors, data managers, and the statisticians will be separated from the study team and the participants until statistical analysis are complete.

2.7. Interventions

2.7.1. Intervention group: moxibustion intervention + conventional intervention

Moxibustion practitioners who are registered with the National Health Commission of the People's Republic of China will perform moxibustion intervention for participants in this study. All moxibustion practitioners must complete 8 years of Chinese Medicine University's master degree education and have over 5 years of specific training in the field of rheumatology. Before the beginning of this study, Principle Investigator (PI) of this study will take an educational course to ensure the standardization of moxibustion procedures. Each practitioner will be provided with a booklet describing moxibustion treatment regimens as well as this study protocol. Any moxibustion interventions related problems will be solved by PI via workshops or hands-on training in the next few days.

The selection of acupuncture points will be decided according to TCM meridian theory. AS is known as '*Bi syndrome*' in TCM. From the perspective of TCM, *Bi syndrome* is resulted from the kidney deficiency and cold-damp coagulation in Du meridian of the back. The treatment acupuncture points will be selected based on surveys and expert consultations (professors and researchers in moxibustion), text books, clinical studies, literature reviews, and systematic review studies [33–36]. Thus, three standard acupuncture points Shenshu BL 23, Mingmen DU 4, Yaoyangguan DU 3 and 2 points of '*ashi*' will be chosen as treatment acupuncture points. Shenshu BL 23 is in the bladder channel of the Foot Tai Yin meridian, and is closely related to the kidney and bones. Moxibustion at BL 23 can treat AS because of its function of nourishing the kidney, promoting blood circulation and strengthing the lumbar vertebrae [23]. The DU4 and DU3 acupuncture points in the Du meridian may have an effect on regulating AS due to its role of warming the kidney and expelling cold on bones [37]. The location and TCM theories of acupuncture points are described in Table 2.

Participants in this group will receive moxibustion intervention once a day, seven days a session for three sessions. After three-session intervention, participants will be followed up for six weeks. After sterilizing the skin surface at every acupuncture points, participants will be instructed to stay in the comfortable prone position and fully expose their back for the moxibustion intervention in a therapy room (temperature: 24–28 °C). By referring the previous research [38,39], we will use indirect mild moxibustion devices (Nanyang Hanyi Co., Ltd., Henan, China. 10 mm diameter and 40 mm height). This moxibustion

Table 3
Extending the Consolidated Standards of Reporting Trials (CONSORT) statement to moxibustion.

NO.	Item	Detail	Intervention
1	Moxibustion rationale	1a) Type of moxibustion (e.g., direct moxibustion, indirect moxibustion, heat-sensitive moxibustion, moxa burner moxibustion, natural moxibustion) 1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate 1c) Extent to which treatment was varied	Indirect mild moxibustion The treatment acupuncture points will be selected based on surveys and expert consultations (professors and researchers in moxibustion), text books, literature reviews, and systematic review studies No variation
2	Details of moxibustion	2a) Materials used for moxibustion (e.g., moxa floss, moxa cone, moxa stick, herbal patches, and their sizes and manufacturers) 2b) Names of acupoints (or location if no standard name) for moxibustion (uni/bilateral) 2c) Number of moxibustion units and/or moxibustion time per point (mean and range where relevant) 2d) Procedure and technique for moxibustion (e.g., direct/indirect, warming/sparrow-pecking technique, warming needle, moxa box, heat-sensitive moxibustion) 2e) Responses sought (e.g., warm feeling, skin reddening, burning pain, heat-sensitization phenomenon) 2f) Patient posture and treatment environment	Moxibustion devices made of mugwort with a paper cylinder (Nanyang Hanyi Moxa Co., Ltd., Henan, China. 10 mm diameter and 40 mm height). BL 23, DU 4, DU 3 A total of 3 moxibustion pillars will be attached at each acupuncture point on per treatment session After the moxibustion pillar is adequately ignited and sufficiently combusted for approximately 5 seconds, and then the moxibustion pillar will be put into the moxibustion device and attached at BL 23, DU 4, DU 3 and 'ashi' at the same time. The participants should feel warmth but not scorching heat during the moxibustion intervention. After sterilizing the skin surface at every acupuncture points, participants will be instructed to stay in the comfortable prone position and remove clothing to fully expose their back for moxibustion intervention in a temperature controlled room (25–28 °C)
3	Treatment regimen	3) Number, frequency and duration of treatment sessions	Participants in the intervention group will receive moxibustion intervention once a day, 7 days a session for a total of 3 sessions. After 3-session treatment, participants will be followed up for 6 weeks.
4	Other components of treatment	4a) Details of other interventions administered to the moxibustion group (e.g., acupuncture, cupping, herbs, exercises, lifestyle advice) 4b) Setting and context of treatment protocol, and information and explanations to patients	Conventional medications, Educational booklet, Psychological counseling and relaxation exercises weekly, Self-exercise programme three times a week Before study participants will be agreed to enter in this clinical trial, researchers must explain to the participants all about the clinical trial purpose, outcome measurements, benefits, potential adverse events and responsibilities during the trial
5	Treatment provider background	5) Description of treatment provider (qualification or professional affiliation, years in moxibustion practice and other relevant experience for professional, or any special training in advance for layman)	Moxibustion treatment will be performed by Chinese Medicine (CM) practitioners who are registered and certified by the Ministry of Health of the People's Republic of China. All project practitioners will have at least 3 years of specific moxibustion training in the field of rheumatology and will have received more than 8 years of Chinese Medicine University's master degree education.
6	Control and comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify the choice 6b) Precise description of the control or comparator. If another form of moxibustion or moxibustion-like control is used, provide details as for Items 1 to 3 above	According to pragmatic design, the control group will receive routine therapies for ankylosing spondylitis. We do not include other forms of moxibustion in this research
7	Precaution measures	7) Precise description of the precaution measures, if any	In order to prevent burns, the participants should feel warmth but not scorching heat during the moxibustion intervention. If participants feel a burning sensation, a new moxibustion pillar will be replaced immediately by the moxibustion practitioner at the same acupuncture points.

device has two parts: a paper cylinder covered with mugwort and an adhesive membrane on the bottom. Mugwort is placed in the device after it is adequately ignited and sufficiently combusted for approximately 5 s. Then, the moxibustion device will be attached at BL 23, DU 4, DU 3 and '*ashi*' at the same time. The heat sensation of moxibustion is gradually increased to induce a mild warm '*DeQi*' sensation to patient. In order to prevent burns, the participants should feel warmth but not scorching heat during the moxibustion intervention. If participants feel a burning sensation, the moxibustion practitioner at the same acupuncture points will replace with a new moxibustion device immediately. Moxibustion at each acupuncture point will last approximately 10 min. In each treatment session, about three moxibustion pillars will be attached at each acupuncture point. Thus, the entire time of moxibustion intervention process for each patient will last for about 30 min. Moxibustion intervention details based on the CONSORT statement to moxibustion are shown in Table 3. In addition, participants in this group will also receive the conventional intervention from the control group.

2.7.2. Control group: conventional intervention only

According to a pragmatic design, conventional interventions will include as below: 1) Conventional medications (NSAIDS, DMARDs, biological agents, etc.) prescribed by the rheumatologist in charge according to the Assessment of Spondylo Arthritis International Society/European League Against Rheumatism [40]. Moreover, participants will be encouraged to record any new modalities during the clinical trial. The research will collect these data during the trial visit period. 2) Educational booklets including information about anatomy of the spine and normal spine movements, symptoms and prognosis of AS, proper diet for AS, importance of alcohol and tobacco avoiding, sexuality and pregnancy for AS, rest and how to reduce the back pain [41]. 3) Psychological counseling and relaxation exercises weekly. 4) Self-exercise programme: Self-exercise programme will involve stretching, mobility, spinal extension, and range of motion (ROM) exercises. Participants will be encouraged to continue these exercises for three times a week.

2.8. Outcomes

2.8.1. Primary outcomes

- Physical function: Bath Ankylosing Spondylitis Functional Index (BASFI), as a quick and simple self-reported instrument, was used to detect the functional anatomy of AS patients. The BASFI index is comprised of ten items. A horizontal 0–10-cm line measured each item (0 = easy to perform, 10 = impossible and difficulty to perform). The first eight-specific items were designed to evaluate respondents' perception of their functional abilities and physical capacity and additional two items were designed to determine patient's ability of physical function in daily life [42]. Chinese versions of BASFI index proved to be reliable and valid [43]. The Chinese version of the BASFI will be assessed at three time points (baseline, primary endpoint-week 4 and follow-up point-week 6).
- Disease activity: Bath Ankylosing Disease Activity Index (BASDAI), as a validated self-assessment tool, was used to measure the disease activity of AS patients. The BASDAI index is consisted of six items (duration/severity morning stiffness, spinal pain, pain/swelling in other joints, fatigue and peripheral entheses). Like BASFI, a horizontal 10-cm line measured each item (0 = none, 10 = very severe symptoms) [44]. Additionally, the Chinese version of the BASDAI proposed by Professor Lin has been employed, and the Cronbach's α of the BASDAI has been previously reported to be between 0.90 and 0.95 [43]. We will therefore assess participants at three time points (baseline, primary endpoint-week 4 and follow-up point-week 6).
- Spinal mobility: A Chinese version of the Bath AS Metrology Index (BASMI) will assess the spinal mobility of AS patients [43]. This questionnaire consists of five dimensions (lateral flexion, Schöber test, cervical rotation, intermalleolar distance, forward flexion). Each dimension will be assigned a score ranging from 0 to 2, with final sum scores ranging from 0 to 10. We will therefore assess participants at three time points (baseline, primary endpoint-week 4 and follow-up point-week 6).

2.8.2. Secondary outcomes

- HRQoL: Health-related quality of life (HRQoL) will be assessed at three time points (baseline, primary endpoint-week 4 and follow-up point-week 6). (i) The SF-36 is a reliable and valid generic health status instrument [45]. Not only participants' physical functioning but also mental health, role-physical, social functioning, bodily pain, role-emotional, general health and vitality components will be checked with the SF-36. (ii) The Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), as a validated and disease-specific tool, was designed to measure HRQoL of AS patients. This tool contains 18 dimensions. Each dimension will be assigned a score ranging from 0 to 1, with final sum scores ranging from 0 to 18 [46]. Moreover, Zhao et al. has developed a good reliability and construct validity Chinese version of the ASQoL [47]. (iii) EuroQol-5 dimension (EQ-5D) is a self-report questionnaire to evaluate HRQoL of AS patients [48]. This questionnaire comprises two parts: (1) five questions assessing different dimensions of HRQoL; (2) visual analogue scale (EQ-5D VAS) from 0 mm to 100 mm.
- Laboratory examinations: A serum sample will be collected at the baseline and the primary endpoint to measure the levels of ESR and CRP. ESR (mm/h) and CRP (mg/l) levels will be determined using the Westergreen method and immunoturbidimetry, respectively. Therefore, we can evaluate serum inflammation biomarkers after moxibustion interventions.

2.9. Safety and adverse events

For safety assessment, this research will check the blood test (routine blood tests, liver function tests, electrolyte analysis, etc.) vital signs, urinalysis, and electrocardiogram (ECG) during the screening period. The probable adverse events following moxibustion intervention include allergic reactions, burns, redness and infections [49,50]. To avoid potential adverse events, any unexpected and unintended responses will be encouraged to report by participants during the clinical trial process. Moreover, the research team member will also perform safety assessment three times per week by visiting the participants. The presence of symptoms, the date of occurrence, duration and severity of adverse events, suspected causes and the correlation with the treatment will be carefully recorded in CRFs by the research team member. PI in the research team will judge these adverse events according to WHO 5-grade performance status classification. If severe adverse events occur, PI should report to IRB and suspend all clinical interventions immediately.

2.10. Statistical methods

2.10.1. Sample size

Sample size will be calculated by NCSS-PASS (NCSS, LLC, Utah, United States). We will refer to the previous moxibustion case report under the BASFI as the primary outcome which is in line with our research [35]. The parameters will be set as follows: $\alpha = 0.05$, power ($1-\beta$) = 0.9, mean difference = -0.65, standard deviation (SD) = 1. Thus, this clinical trial will require 100 participants (50 participants per group) with a 20% loss to follow up.

2.10.2. Statistical analysis

A medical statistician blinded to the group settings will perform the data analysis. The whole statistical analysis will be performed on an intention-to-treat (ITT) basis using the SPSS 22.0 software package (SPSS Inc., Chicago, IL, USA). Demographic data will be elucidated as frequency (percentage) for categorical data and mean value ± standard deviation for continuous data. The variables will be investigated using the Shapiro–Wilk test to determine whether or not they are normally distributed. After testing for normal distribution, continuous normally distributed variables (age, disease duration, BMI, income, education, etc.) will be compared by independent t-test. Otherwise, continuous non-normally distributed variables will be compared by independent samples Mann–Whitney U test. The chi-square test or Fisher's exact test will be performed for categorical variables (gender, smoking, medication, marital status, etc.). Repeated measures analysis of variance (ANOVA) with time (the baseline, primary endpoint, follow-up point) as a within-subject factors and treatments (moxibustion intervention + conventional intervention vs conventional intervention alone) as the between subject factors will be used to analyze the dependent variables BASFI, BASDAI, BASMI, ASQOL, EQ-5D and SF-36. If differences between groups were identified, the Bonferroni method of post hoc multiple comparisons will be conducted. Missing data will be assessed using a multiple imputation adjustment approach. A value of $p < 0.05$ (2-tailed) will be accepted for this study.

2.11. Data management

Before recruitment, research team members will participate in a training meeting about the data management and measurement standardization. After completing this clinical trial, assessors and research assistants must hand over original CRFs to data administrators and data administrator also must ensure that no records will be missed in CRFs. Then, according to a standard protocol for data entry, data will be double-entered by data administrators blinded to the group allocation and the source of any inconsistencies will be explored to compare with the original CRFs. An independent statistician who is blind to the clinical trial will comprise statistical analysis. To protect confidentiality, written data will locked in a cabinet at the TCM clinical and research center with limited access and electronic data will be secured using a password. All research archives will be protected for at least 5 years in the study site.

2.12. Ethics and study registration

To protect human participants, this protocol has been approved by the Institutional Review Board (IRB) of Affiliated Hospital of Nanjing University of Chinese Medicine in March 2018 ([2018] YK006-01). In addition, this protocol will be conducted according to WHO Good Clinical Practice (GCP) standard and the Declaration of Helsinki [51]. Before study participants will be agreed to enter in this clinical trial, researcher team members must explain to the participants about the purpose of this study, outcome measurements, benefits, potential adverse events and responsibilities during the trial. Before any clinical work commences, all study participants will sign a written informed consent. This protocol has been registered with the Acupuncture-Moxibustion Clinical Trial Registry (AMCTR-IPR-18000206).

3. Discussion

Moxibustion has been proven to ease the pain and improve physical functional of AS patients in East Asia countries [24]. Previously, some clinical trials [52,53] were conducted to assess the efficacy of moxibustion for the management of AS. The results of these trials showed that, a cointervention of moxibustion and NSAIDs therapy played a positive effect on improving treatment efficacy of AS [52,53]. However, the random sequence generation was not reported adequately in all clinical trials, which may be result in selection bias [25]. Moreover, no previous clinical studies mentioned the use of blinded assessors and sample size calculation. Thus, due to the methodological flaws from previous clinical trials, whether moxibustion is an effective intervention for AS remains controversial. In this research, we will adopt a rigorous clinical trial design based on Extending CONSORT statement to moxibustion and SPIRIT 2013 guidelines to reduce previous possible risk bias.

Previous studies [52,53] only adopted the TCM measurement –treatment efficacy as the primary outcome for measuring the effect of moxibustion for AS. However, this Chinese culture-specific efficacy measurement cannot avoid bias from the moxibustion practitioners [54]. Thus, apart from simple evaluation of the treatment efficacy, this study will use international validated assessment tools (BASDAI, BASFI, BASMI and HRQoL: SF-36, EQ-5D, ASQoL) to reduce detection bias and show results more comprehensively [55]. These various measurements may provide multidimensional perspectives to explore the efficacy of moxibustion intervention for AS more comprehensive. In clinical practice, multiple factors may contribute to the effect of moxibustion, including stimulating methods, frequency, duration, and the moxibustion sensations experienced. Thus, we will use manufactured moxibustion of standardized quality to reduce the heterogeneity in our research [39]. Previously, incidence rates of adverse events regarding moxibustion interventions were low and the majority of adverse events were only minor adverse events [50]. However, a recent study showed that approximately 47% of participants who received moxibustion intervention experienced moderate-to-severe adverse events (mostly burn wounds) [50]. Thus, for the safety assessment of moxibustion interventions, our research will report all details about any adverse events. This will be a strong point of this study.

In order to avoid potential bias and detect specific effects of moxibustion, it is encouraged to apply sham moxibustion devices in the clinical practice. Currently, one sham moxibustion device have been proposed for trials of moxibustion, and this may mask participant and practitioner during the moxibustion process [28,56]. In addition, because of the high prevalence and common knowledge of moxibustion intervention among patients from East Asia countries, it is difficulty to make the double-blinding by means of sham moxibustion devices. Recently, Lee et al. [57] performed a double-blinded clinical trial to assess the effect of a real moxibustion device with a placebo moxibustion device. However, the majority of participants in their research were able to determine the difference between the real moxibustion device and the placebo one. Additionally, recent reports showed that expectation of the effect of moxibustion and enhanced doctor–patient relationships may also contribute to placebo effects during the moxibustion intervention process [58]. In Asia, it is very common that participants show their high expectations and beliefs of moxibustion efficacy and make frequent interpersonal communications with their moxibustion practitioners [59]. Furthermore, Liang recommended that it was possible to add moxibustion intervention to NSAIDs to minimize the treatment course of the pain and reduce the costs of medical care [60]. As a result, in order to improve applicability of moxibution to the clinical field, it is more appropriate to use a pragmatic design, rather than a certain moxibustion sham device to examine the effectiveness of moxibustion for AS [61,62]. Similar study designs have been detected in another moxibustion clinical trial [63].

This study has several limitations. First, we will be unable to blind moxibustion practitioners and participants due to the nature of moxibustion intervention. To minimize other bias that can occur during the trial, outcome assessors and data analysts will be blinded. All moxibustion practitioners will receive educational trainings and PI in this study will make a strict quality control. Second, high-drop rates may be another limitation of this clinical trial. According to the previous, over 40% of patients discontinued the moxibustion intervention before they finished follow-up periods screening due to the high cost of treatment and long period of treatment time [64]. In our research, we have to face the same challenges. Thus, in order to reduce drop-out rates, research team members will provide 50$ as financial compensation for participants. In addition, we will perform moxibustion treatment for a short-period of time and to follow-up after 6 weeks according to experts' suggestions. Third, the study population of this study will comprise of only Han Chinese ethnicity. In the future, participants of different backgrounds should be included to examine the effects of moxibustion for AS.

4. Conclusion

In conclusion, this research is a protocol for an open, assessor- and analyst-blinded, randomized clinical trial with two parallel groups to assess the efficacy and safety of moxibustion for AS. Results of this preliminary study will provide essential information for the design of future, large-scale, clinical trials. We hope that this trial will contribute to helping moxibustion practitioners to make decisions regarding the use of moxibusiton for AS in the clinical practice.

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Conflict of interest statement

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eujim.2019.02.005.

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