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A study protocol for a randomised controlled trial on the efficacy of yoga as an adjuvant therapy for patients with Ankylosing spondylitis amidst COVID-19 pandemic

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ABSTRACT

Background: Amidst the adversities of the COVID-19 pandemic, the health care system has seen a new paradigm shift towards e-health or telehealth services. In the advent of catering to the geometrically increasing health care needs of the patients suffering from various chronic health conditions when in social isolation, the need for such shifts is paramount. Patients with Ankylosing spondylitis using immunosuppressants with variable degrees of disabilities are at higher risk from this isolated status. This study aims to assess the efficacy of e-Yoga as a treatment option for these patients.

Methods: The proposed study is a single-center, parallel-group prospective randomized, open-blinded end-point trial. Patients aged between 30 and 50 years will be recruited from the members of Antardhwani: A society of ankylosing spondylitis based in Ahmedabad, Gujarat. Yoga experts will administer a scientifically developed and validated Yoga module via e-Yoga modalities. A total of 135 patients will be recruited and randomly allocated to Yoga and control groups. Data will be recorded at baseline and three months on disease activity, degree of functional limitations in patients, quality of life, inflammatory biomarkers, depression, and anxiety using Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), AS Quality of Life index (ASQOL), C reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Physical health questionnaire-4 (PHQ-4), respectively.

Discussion: The study will report the efficacy of e-Yoga in catering to the physical and mental insufficiencies of inpatients with Ankylosing spondylitis amidst COVID-19 pandemic. The study is prospectively registered in the Clinical Trial Registry of India (CTRI/2020/08/027215)

1. Introduction

When a third of the global population is still under social isolation, the COVID-19 infection has unfolded catastrophic consequences upon vulnerable populations. “Stay Home, Stay Safe” may be a wide-reaching mitigation effort to control the outbreak, but home is not always a safe or healthful space for vulnerable populations. Patients with underlying rheumatologic disorders and under immunosuppressant drugs are reported to be at higher risk in isolated circumstances. In addition, social distancing norms necessitating confinement have instigated physical inactivity, changed dietary habits, psychological apprehensions, and poor management of co-morbidities that may exacerbate medical conditions and worsen chronic disease. Ankylosing spondylitis (AS) is a chronic inflammatory disease with prevalence per 10,000 as 16.7 in Asia and a total number of cases ranging from 4.63 million – 4.98 million [1]. AS is an autoimmune disease marked by profound inflammation at the axial and sacroiliac joints. Patients with AS have physical disability, poor work efficiency or unemployment, increased need for medical attention, psychological distress, and low quality of life [1,2]. Although the exact pathology of AS remains

Abbreviations: AS, Ankylosing Spondylitis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; PHQ-4, Physical Health Questionnaire - 4; ASQOL, Ankylosing Spondylitis Quality of Life

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unclear, a cascade of events linking HLA-B27, inflammatory markers, cytokines (TNF alpha and IL 10), genetic and environmental factors suggest autoimmune mechanisms behind its pathogenesis [3]. Management of AS involves administering anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs, etc., with limited effect on the disease progression. A recent report highlighted the positive relationship between perceived COVID-19 threat and psychological status with the disease activity among AS patients [4]. However, with emerging knowledge in this domain and new scientific technologies, it is noteworthy how the role of intervention such as exercise, physiotherapy, and mind-body medicine is being increasingly recognised to be an efficient adjuncts in treating AS [5,6]. Previous study suggests an improvement in the Bath Ankylosing spondylitis disease activity index (BASDAI) by 32%, advocating the effectiveness of yoga and physiotherapy intervention in these patients [7]. Yoga, a mind-body medicine, has been observed to curtail chronic pain, functional disability, improve joint mobility, reduce inflammation, improve mental health and the overall quality of life [8–11]. However, the evidence for the effectiveness of yoga-based intervention in patients is sparse, and for e-health yoga interventions even sparser. The present study is designed to impede this gap and depict the feasibility and efficacy of yoga as a potent treatment modality for AS amidst the COVID-19 Pandemic.

2. Methods

2.1. Overview

Approximately 135 patients with AS will be randomized in a 1:1 allocation ratio in the study and control groups. The study group will receive a 60-minute online yoga-based intervention and the standard care for AS, whereas the control group will receive standard care only. The study aims to evaluate pain, quality of life, spinal flexibility, disability, and inflammatory markers in patients with ankylosing spondylitis at baseline and three months post-randomization. The protocol of the study is drafted following the Standard Protocol Items: Recommendations for Interventional Trials [12]. The study has been approved by institutional ethics committee, and the study is prospectively registered in the Clinical Trial Registry of India (CTRI/2020/08/027215).

2.2. Study design and setting

The trial will be a single-center, parallel-group prospective randomized, open-blinded end-point trial (PROBE) to evaluate yoga-based intervention's efficacy among patients with Ankylosing spondylitis. (Fig. 1 Trial profile). The patients will be recruited from the pool of members of Antardhwani: An Ankylosing spondylitis society based in Ahmedabad, Gujarat, which is working towards management of AS. The intervention was designed to be given virtually in the form of e-Yoga by the yoga experts at S-VYASA University, Bangalore. The researchers will administer the assessments at baseline and three months through online mode.

2.3. Participants

Patients aged between 30 and 50 years, both genders with a minimum AS history for three years and fulfilling the New York's criteria for Ankylosing spondylitis [13], will be recruited. Each patient will be followed up for three months. Exclusion criteria include (a) Severe disability, (b) Patients with neurological deficits, (c) Patients with cardiac compensatory conditions, (d) contraindications to yoga and exercise testing, (e) History of recent major surgery, (f) participating in any other trial, receiving any additional complementary therapy, and (g) participant practicing yoga before the recruitment in the study (h) Patients with a psychiatric diagnosis. Eligible patients providing informed consent will be randomized into two groups with an allocation ratio of 1:1, i.e., the Intervention and Control arm.

2.4. Sample size

The sample size was calculated using G power software as 108 (Yoga=54; Control=54). The effect size taken was 0.63 from previous studies and fixing $\alpha = 0.05$ [14]. With a power of the study considered 0.90 and a dropout rate of 20%, a total sample size of 135 subjects was calculated for the current trial.

2.5. The intervention group (Yoga Group)

The intervention group will be taught yoga practices additionally by institutionally trained and certified yoga therapists with over five years of experience through e-health modalities (online video classes). The standard medical care will be continued for all the patients during the study period. The current yoga module was developed keeping in mind the COVID-19 pandemic and following focused group discussions between our multidisciplinary team, including experts from rheumatology, physiotherapy, medicine and yogic sciences, based on the pathophysiological mechanisms involved in disease causation, progression, and the available literature in yoga. Later the protocol was also validated by the yoga professionals of different schools across India.

The yoga module comprises a combination of yoga postures, breathing practices, meditative techniques, and relaxation (Table1). The physical postures consist of preliminary stretching exercises followed by breathing exercises and then by *asana* in four categories (standing, sitting, prone, and supine) followed by *pranayama*. It provides a moderate intensity of physical activity. The patients will be instructed to follow a specific breathing pattern, culminating in a relaxation response during the practice. The practices are well spaced by relaxation techniques to avoid any strain or exhaustion to the patients. No substantial modifications were needed in the yoga module while teaching the practices to the patients as the module was developed, keeping in mind their needs and condition.

During the study duration, the subjects will be contacted by the researcher, assessed, and randomized. Following which the intervention group will undergo online yoga sessions four times a week for 60 min each for three months. Each session will have a pre-planned, validated yoga protocol which will be rendered to the patients by the yoga experts. During the non-contact period, the subjects will be encouraged and motivated to practice the yoga protocol for the remaining days at home three times a week for 60 min during the study. Video of the complete session and picture-based modules will be given to assist the home-based practices. Besides, each patient, irrespective of their group allocation, will be provided a booklet explaining the disease, prognosis, details of the yoga module, and its health benefits pictorially. In addition, a logbook will be given to all recruited participants to record their practice at home, including the duration and time of practice, additional physical activities, and medication intake to document their adherence. The consultants viewed 10% of the videotaped sessions and reported satisfactory fidelity towards the intervention administration.

2.6. Standard medical care

The trial's objective is to evaluate the effect of yoga-based intervention as an adjuvant to the standard medical care provided by treating physicians. The investigators have made additional efforts to ensure that each subject of the trial receives similar medical care. Due to the pandemic, the standard care will be limited to the medications and physiotherapy prescribed by the treating physician.

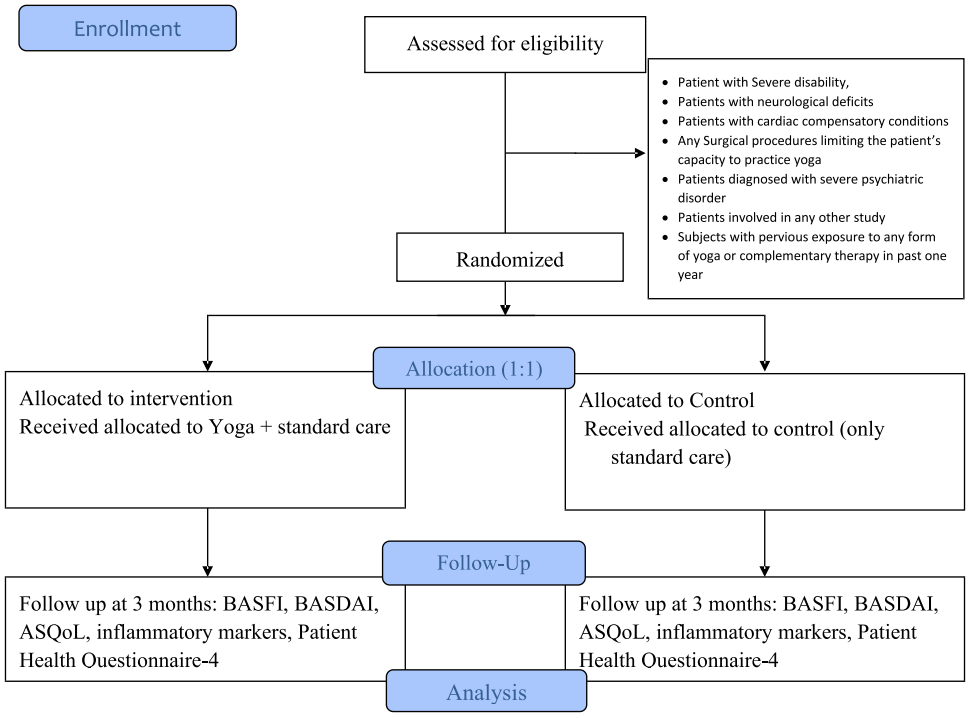

Fig. 1. Trial profile of the study

Table 1
Yoga module for patients with ankylosing spondylitis.

Sl. no.	Practice	Duration (60 min)
1.	**Loosening practices (Sukshma Vyayama)** • Neck movement (Front-back- side bending, twisting & rotation) • Shoulder rotation • Twisting • Side bending • Alternate straight leg raising • Vertical stretch of the knee • Vertical stretch of the knee both legs • Pavanmuktasana Lumbar stretch (Single & both legs) • Dorsal stretch • Alternate foot knee lumbar stretch • Side leg raising • Side Lumbar stretch	17 min
2.	Instant relaxation technique	2 min
3.	Breathing ExercisesHands in &out breathingHands stretch breathing Tiger breathing Shashankasana breathing on chair Lumbar stretch breathing	10 min
4.	**Chair suryanamaskara**	6 min
5.	**Asanas** • Tadasana • Ardhakati Chakrasna • Ardhachakrasna • Marjariyasana (Cat pose) • Makarasana • Bhujangasana • Salabhasana	7 min
6	**Pranayama** • Sectional breathing • Nadisuddhi • Bhramari • Nadanusandhana	8 min
7.	**Deep relaxation technique**	10 min
8.	**Total duration**	60 min

Each subject and the accompanying family members will be educated regarding the risks and disabilities related to the progression of the disease.

2.7. Control group

The control group will be advised to continue the standard medical care for the same duration, i.e., three months. In addition, an educational session pertaining to the significance of medication, additional physical activity, dietary changes, etc., will be conducted at baseline. The control group will also be provided with a logbook to record their physical activities and medications intake.

2.8. Termination criteria

Participants will be withdrawn from the trial if they acquire COVID-19 infection as it may cause a cytokine storm. In addition, the subjects will not be able to follow the protocol as well, as it may bring changes to the trial's objectives.

2.9. Randomization and blinding

All subjects will be randomized into two groups, the Yoga group and the Control group, with an allocation ratio of 1:1. An independent statistician will generate a computerized unpredictable random number sequence using randomizer.org, who has no role in the current study. Further, sequentially numbered opaque sealed envelopes will be maintained by a person who is not a part of the study to maintain concealment. Blinding of the patients is not possible in this trial; however, the outcome assessor will be blinded.

3. Outcome measures

3.1. Bath AS Disease Activity Index (BASDAI)

This is the gold standard for measuring and following disease activity in AS. It uses a 10 cm visual analog scale to answer questions related to fatigue, spinal pain, Joint pain/ swelling, Areas of localized tenderness, and morning stiffness. The final score ranges from 0 (best) to 10 (worst) [15].

3.2. Bath AS Functional Index (BASFI)

It is a set of 10 questions designed to determine the degree of functional limitations in patients with AS. It is measured using a visual analog scale (ranging from 0 being easy to 10 being impossible) and the questions focus on the patient's ability to perform specific functional tasks [16].

3.3. AS Quality of Life index (ASQOL)

An 18-item questionnaire that assesses the quality of life of Ankylosing spondylitis patients. It is a validated tool with a high test-retest reliability and Cronbach alpha coefficients [17].

3.4. C-reactive protein

|C-reactive protein (CRP) blood tests are commonly used to detect increased protein levels in the blood. CRP is valued clinically as a sensitive marker of inflammation. CRP Levels in young, healthy adults are usually less than ten mg/L, but more than that can increase response to infection or inflammation [18].

3.5. Erythrocyte sedimentation rate (ESR)

A blood test is commonly used to detect increased protein in the blood. If specific proteins cover red cells, these will stick to each other and cause the red cells to fall more quickly. So, a high ESR indicates inflammation somewhere in the body. Normal range is 0–22 mm/hour for men and 0–29 mm/hour for women [19].

3.6. Patient Health Questionnaire-4

A four-item questionnaire was used to briefly and accurately measure the core signs and symptoms of depression and anxiety. A score of 3 or more on depression and anxiety subscales identifies potential cases of depression and anxiety, respectively [20].

3.7. Blood sample collection

Blood samples (5 ml) will be collected aseptically in the plain tube and standardized laboratory procedures for hs-CRP and ESR. The samples will be collected before the intervention commencement (Day of randomization ± seven days) and after three months (3 months ± seven days) of baseline data collection.

4. Statistical analyses

Baseline participant characteristics of both the group will be presented. The normality of the variables will be assessed using the skewness statistic and normal probability plot, based on which appropriate parametric or nonparametric tests will be used. Follow-up data at three months will be explored through linear mixed models utilizing repeated measures analyses, allowing simultaneous modeling of the two outcome time points. Subgroup analyses will be done based on groups, adherence to the intervention, and other clinical data. An intention-to-treat analysis will be conducted along with a separate per-protocol analysis, as adherence may be suboptimal. All statistical tests will be two-tailed and statistical significance will be set at 0.05. The final report will follow the CONSORT 2010 guidelines as well as its extension to non-pharmacological interventions [21,22].

5. COVID-19 and Tele-yoga

The trial was initiated in April 2020 amidst the COVID-19 Pandemic. The protocol was amended as per the Indian Council of Medical Research Guidelines for research guidelines during COVID-19 [23]. The contact sessions were converted into online sessions. The follow-up was also done in online mode, and the investigators took blood samples from home. Additionally, bi-weekly calls were also made to improve adherence during the non-contact period. Patients infected with COVID-19 will be excluded from the trial as they may have an additional cytokine storm, leading to changes in the CRP and ESR.

6. Discussion

The current study is the first study to explore the effect of yoga rehabilitation on the physical functioning and psychological well-being of patients with AS amidst the COVID-19 pandemic compared to a control group. In this protocol, we have highlighted the design of the study and the precautions taken keeping the COVID-19 pandemic in mind. Under the shadow of COVID-19, social confinements have instigated physical inactivity, faulty dietary habits, psychological apprehensions. During this time, yoga -being an indoor activity and requiring less space to practice - may act as a pan-pharmacon for all the symptoms of AS. Potential strengths of this study are (1) First RCT to evaluate the efficacy of yoga for AS patients, (2) conducted amidst COVID-19 pandemic which will allow us to evaluate the efficacy of yoga in AS patients in these unprecedented times, (3) understanding the complete physical and mental effect of Yoga in AS patients. Some possible limitations are also acknowledged, including complete online sessions, which was a must to conduct the study amidst the pandemic, (2) the study did not involve any inflammatory cytokines, which might have given a detailed understanding of the efficacy of yoga. In the current study, the recruitment of the patients is expected to be completed by April 2022. The results will be reported in the scientific media through research articles and conferences. The preliminary results will be available from the corresponding author on reasonable request. The details of the individual patient will be kept confidential.

Grant support or other sources of funding

The current trial is not a funded trial.

Ethical statement

The authors declare that the trial is ethically approved, and consent from the participant will be obtained.

Declaration of interests

The authors declare no conflict of interests.

Authors statement

On behalf of all the authors, I state that all the queries raised by the reviewers and the editors have been addressed.

Ethics and dissemination

Research ethics approval

The trial was submitted and approved by the institutional ethics committee at SVYASA University.

Protocol amendments

No amendments were made in the protocol.

Consent or assent

Consent forms were signed by the subjects before the recruitment in the study.

Confidentiality

Data was stored securely, and anonymity of the patient's identity was ensured by allocating them patient's IDs instead of using their names.

Access to data

The investigators in the study have access to the data, which can be made available once the study is complete if needed.

Ancillary and post-trial care

The patients were encouraged to practice Yoga even after the study. However, no post-trial care was specifically provided.

Dissemination policy

The study data will be reported, published in scientific journals, and presented at the conference.

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