The Feasibility and Acceptability of Acupressure in Patients with Rheumatoid Arthritis

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Research Design - Study Protocol: Feasibility and Acceptability of Acupressure in Patient with Rheumatoid Arthritis

1.1 Objective

The purpose of this pilot study is to assess the feasibility and acceptability of acupressure in patients with rheumatoid arthritis (RA). This study will allow us to better estimate the needed sample size and to focus on specific primary outcome measures for future studies.

1.2 Specific Aim/Hypothesis

(1) Aim 1: Determine the feasibility and acceptability of self-performed acupressure in patients with RA.

(2) Aim 2: Assess the impact of acupressure of the pain, fatigue, and sleep of patients with RA.

(3) Aim 3: Assess the impact of acupressure on disease activity in patients with RA.

1.3 Background Information

Acupuncture is a component of Traditional Chinese Medicine wherein thin needles are inserted at specific points on the body (acupoints) to treat disease. Research over the past three decades has shown that acupuncture is effective for the treatment of chronic pain (for recent meta-analysis see[1]). Acupressure is a related technique wherein pressure is applied via a finger or device to specific *acupoints*. Acupressure is highly scalable and can be taught to patients (for self-application) and supported by the use of technology. While less research has been performed on self-applied acupressure, emerging data indicates that self-acupressure is effective for chronic pain.[2-7] In our own studies, we completed a randomized clinical trial in 288 fatigued breast cancer survivors who self-administered acupressure (as proposed in this application) and found significant improvements in pain, fatigue, sleep, and depression.[8, 9] We also recently completed a randomized controlled trial of our acupressure intervention in 67 chronic low back pain patients randomized to either acupressure or usual care. In that pilot study, self-acupressure reduced low back pain more so than usual care (35% reduction, $p<0.05$) after 6 weeks of treatment.

RA is the most common inflammatory arthritis with a prevalence of 0.5-1% in the United States.[10,11,12] RA is a symmetric polyarthritis characterized by synovitis and systemic inflammation. RA associated with significant morbidity, chronic disability, pain, stiffness, sleep disturbance and increased rates of depression. [13]

Acupuncture is thought to help in RA. In a meta-analysis of 43 studies of complementary and alternative medicine in RA patients, acupuncture was able to improve quality of life in 42 studies.[14] Acupuncture has been recommended via professional agreement as a non-drug

intervention in RA.[15] These data support the proposal of using self-acupressure as an intervention to treat the symptoms of RA.

Acupressure has never been studied in RA. The purpose of this pilot study is to assess the feasibility and acceptability of acupressure in patients with RA.

1.4 Methodology

This will be an open feasibility study of 30 subjects conducted at the University of Michigan

1.4.1 Participants. We will enroll 30 adults (age 25-75) with a RA diagnosis from the Rheumatology Clinics at UM primary and satellite sites. Detailed inclusion and exclusion criteria and rationale for exclusions are detailed below.

Inclusion:

- Patient is being treated for RA at a Rheumatology Clinic at the University of Michigan or another by rheumatologist and reports being prescribed at least one of the following medications:
    - Methotrexate (Trexall, Rheumatrex)
    - Hydroxychloroquine (Plaquenil)
    - Sulfasalazine (Azulfadine)
    - Leflunomide (Arava)
    - Tumor necrosis factor inhibitor (TNFi), including:
        - Adalimumab (Humira)
        - Etanercept (Enbrel)
        - Certolizumab pegol (Cimzia)
        - Golimumab (Simponi)
        - Infliximab (Remicade)
    - Abatacept (Orencia)
    - Tocilizumab (Actemra)
    - Janus kinase inhibitor (JAKi), including:
        - Tofacitinib (Xeljanz)
        - Baracitinib (Olumiant)
        - Upadacitinib (Rinvoq)
    - Rituximab (Rituxan)
- Ages 25 – 75

Exclusion:

- Visual or hearing difficulties that would preclude participation,
- Do not speak or read English
- Do not have access to smart phone with access to mobile applications
- Severe psychiatric disorders including history of substance abuse disorders,
- Individuals on high doses of opioids (over 100 OME per day),

- Taking blood thinners, including warfarin (Coumadin), dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), or betrixaban (Bevyxxa)
- Thrombocytopenia (low platelet count)
- Expecting to receive surgery within the next year for their RA
- Pregnancy or breast feeding, or anticipate pregnancy in next year,
- Actively applying for disability or compensation, or actively involved in litigation.
- Anything at the discretion of the PI or study team

1.4.2 Assessments. Pre-screening and recruitment will occur virtually or in-person in clinic. Trained study staff may perform consent in-person at the time of recruitment if feasible and desired by the patient. The study visit will occur at the Chronic Pain and Fatigue Research Center, University of Michigan at Domino Farms. At the initial visit, Day 0, the informed consent process conducted by trained study staff, if not already completed. This will be followed by questionnaire completion using Qualtrics electronic data capture system, and orientation and training on the acupressure device and ambulatory mobile support technology. Table 1 indicates the timeline of the study and when questionnaires will be administered throughout the study. Day 1 treatment will occur via Zoom with the participant and a study coordinator. The participant will perform the treatment with the coordinator observing the technique and available to answer any questions the participant may have.

Participants will be provided with a pre-addressed, pre-paid box to return the AcuWand or may return it in person to the study team at Domino's Farms.

Table 1: Timeline of Study

	Day 0	Day 1	Day 7	Day 21	Day 42	Day 63
	Initial visit					
Screening (if not done)	X					
Consent (if not done)	X					
Treatment		X-Zoom	X	X	X	
Questionnaires:						
Past Med/Surg Hx	X					
PROMIS 29+2	X			X	X	X
FMS	X			X	X	X
HAQ	X			X	X	X
RA disease activity	X			X	X	X
Desire for relief	X					
Expected relief	X					
Credibility					X	
Tolerability				X	X	
Acupr. sensation				X	X	
PGIC					X	
Phone call			X			

FMS = Fibromyalgia Survey Questionnaire. HAQ = Health Assessment Questionnaire. Acupr. Sensation = Acupressure sensation. PGIC = Patient Global Impression of Change.

Clinical data. Participants will undergo an assessment of past medical history and pregnancy status. Medications (*especially analgesics including opioids*), diagnoses, pain interventions, and any relevant labs already collected for clinical purposes will be confirmed via EMR review.

Questionnaires. All participants will complete a battery of validated questionnaires before, during and after completion of treatment intervention. Questionnaires will measure pain, sleep disturbance, fatigue, and depression given the increased rates of these outcomes in patients with RA. Questionnaires will also focus on acupressure expectations, tolerability, and acceptability. Questionnaires will be applied pre-treatment, at 3 and 6 weeks into treatment, and 3 weeks post-treatment intervention (see Table 1). Surveys will be sent via email, and if needed, reminder phone calls will also be utilized.

1.4.3 Study Procedures:

1.4.3a Acupressure Intervention Procedures

Figure 2 Sample MeTime Acupressure App

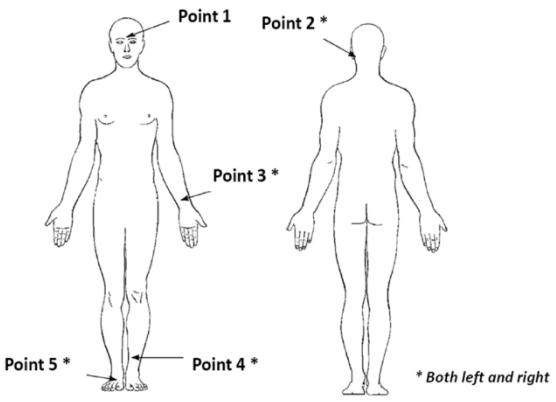
The self-acupressure intervention will be delivered using the modified MeTime Acupressure mobile app in addition to in-person or virtual instruction via study staff. The MeTime Acupressure app was developed in association with patient focus groups (six focus groups each of eight to ten women) and the University of Michigan 3D Media Laboratory (screen shot examples in Figure 2). The MeTime Acupressure app will be loaded onto computer tablets or smart phones by the participants. Participants will also receive an AcuWand to be used in association with the acupressure app to help participants apply the correct amount of pressure to acupoints (See Figure 1).

Figure 1 AcuWand Device

There are 5 acupoints with 4 of the acupoints performed on both the left and right sides of the body (total of 9 points to stimulate; see Figure 3. The relaxing acupoints are:

- *Point 1: Yin tang* (Unilaterally)
- *Point 2: Anmian* (EX17) (Bilaterally)
- *Point 3*: Heart 7 (HT7) (Bilaterally)
- *Point 4*: Spleen 6 (SP6) (Bilaterally)
- *Point 5*: Liver 3 (LV3) (Bilaterally)

Figure 3 Relaxing Acupressure



Participants will be introduced to the MeTime App and AcuWand device at their initial clinic visit. A research team member will provide the patient with instructions and guide the patient through using the app, the AcuWand and performing Self-Acupressure. Study participants will be told to perform acupressure once per day and to stimulate each point a circular motion for three minutes. There are 9 acupressure points, totaling 27 minutes of stimulation per day. Participants will perform daily acupressure for a total of six weeks.

1.4.3b Participant Adherence

Participants will be asked to log time spent using the AcuWand on a daily basis and record any reasons for missed sessions. The Acuwand device also records the time a participant spends using the device.

1.4.3c Standardizing Assessment and Intervention

Fidelity of the acupressure intervention in study staff, who are teaching participants acupressure, i.e., acupressure educators will be assessed by study investigator Rick Harris. Educators will be trained using the Acupressure Therapist Treatment Manual (see supporting documents).

The primary outcome will be the feasibility and acceptability of self-performed acupressure in patients with RA. This will be assessed by the number of sessions completed and the acupressure acceptability questionnaire.

The secondary outcome will be the impact of acupressure on pain. This will be assessed with PROMIS-29+2 questionnaire and the Fibromyalgia Survey Questionnaire.

Exploratory outcomes in this study will include the impact of acupressure on fatigue, sleep, mood, and disease activity in patients with RA. These will be assessed by questionnaires.

1.4.3d Acupressure Benefits

Emerging data indicates that self-acupressure is effective for chronic pain.[2-7] In our own studies, we completed a randomized clinical trial in 288 fatigued breast cancer survivors who self-administered acupressure (as proposed in this application) and found significant improvements in pain, fatigue, sleep, and depression.[8, 9] We also recently completed a randomized controlled trial of our acupressure intervention in 67 chronic low back pain patients randomized to either acupressure or usual care. In that pilot study, self-acupressure reduced low back pain more so than usual care (35% reduction, $p<0.05$) after treatment. We theorize that patients with RA may see benefits in pain, sleep, fatigue, and depression.

1.4.3e Acupressure Risks

Potential Risk – Treatment Interaction – Acupressure. Self-acupressure is a safe intervention. From our previous 3 clinical trials over the past 10 years using this acupressure point formula, we have observed no serious adverse events associated with the study intervention. Our most recent and largest trial of self-acupressure in fatigued cancer survivors (N=288), had 6 adverse events related to acupressure, and all were non-serious cases of mild bruising at acupressure sites. There are no known long-term risks associated with self-acupressure. To minimize the chances of bruising, participants will be trained by the acupressure instructor in how to apply the correct amount of pressure with the AcuWand. Specific attention will be paid to not apply too much pressure. The AcuWand has a built in "buzzer" to notify the study participant when the correct amount of pressure is reached, which will minimize chances of bruising. The participant is free to withdraw from the intervention at any point if the self-acupressure intervention becomes uncomfortable.

1.4.3f Management of expected adverse events

Expected Adverse Event	Criteria for Management	Intervention Modification, if any
Acupressure		
Mild bruising at acupressure sites	Participant verbalizes bruising.	The participant is free to withdraw from the intervention if the self-acupressure intervention becomes uncomfortable.

1.5 Statistical Design

Due to the pilot and feasibility nature of this study, we will primarily be using descriptive statistics. We will obtain pre-, during and post-treatment measures of disease activity and symptoms (pain, sleep disturbance, fatigue, and mood). These measures will be analyzed with t-test or appropriate non-parametric test if data not appropriate. This is an open study.
Aim 1: We will compare number of acupressure treatments performed to the number of total number of sessions required. We would consider successful feasibility to be over 80% of sessions completed.
Aim 2: We will compare scores for pain, fatigue, and sleep on pre-treatment and post-treatment surveys with paired t-test to assess for significance.
Aim 3: We will explore pre-treatment and post-treatment RA disease activity scores with paired t-test to assess for significance.
This is a pilot study and we do not expect that we will achieve statistical significance. With the sample size of 30 we would only be able to detect a difference between pre and post scores would be approximately 0.5 standard deviation.

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