The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with rheumatoid arthritis: a systematic review protocol

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Review question/objective: The objective of this review is to identify and synthesize the best available evidence on the effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with rheumatoid arthritis. More specifically, the review questions are:

- Is acupuncture effective in improving health-related quality of life in patients with RA?
- Is acupuncture effective in relieving pain in patients with RA?
- Is acupuncture effective in improving physical function in patients with RA?

Keywords Acupuncture; pain; quality of life; rheumatoid arthritis

Background

Rheumatoid arthritis (RA) is a chronic inflammatory, multisystemic and autoimmune disease manifested by symmetrical, persistent inflammatory synovitis, involving destructive polyarthritis of the synovium.\textsuperscript{1} According to the World Health Organization data, approximately 1–2\% of all people in the world suffer from RA and its prevalence is about 0.2–0.5\% in Portuguese populations.\textsuperscript{2} The socioeconomic impact is high on the individuals as well as on the health system.\textsuperscript{3}

The conventional treatment for RA has predominantly been the use of non-steroidal anti-inflammatory drugs, including second-generation Cox-2 inhibitors, disease modifying anti-rheumatic drugs and analgesics. Recently, biological agents have been introduced.\textsuperscript{3} However, these type of medication is associated with unwanted side effects, toxicity and limited efficacy.\textsuperscript{4,5} The biological agents have higher costs and the side effects, such as life-threatening infections and increased risk of malignancies, limit their use.\textsuperscript{3} These treatments or surgical interventions are associated with higher costs, unwanted side effects, toxicity and limited efficacy.\textsuperscript{4,6} These and other limitations have led almost 60–90\% of unsatisfied arthritis patients to use complementary alternative medicine, including acupuncture.\textsuperscript{4,5}

Acupuncture is one of the most popular sensory stimulation techniques of traditional Chinese medicine (TCM), originating in China more than 3000 years ago.\textsuperscript{7} It has been recognized that acupuncture stimulates the nervous system and thereby causes the release of neurochemical messenger molecules as well as biochemical changes that influence the body’s homeostatic mechanisms.\textsuperscript{8}

This review will be considered as inclusion criteria; the classical definition for acupuncture that describes the insertion of a metallic needle in TCM points located on the meridians or conduits. However, simple acupuncture can be performed in extra-meridian acupoints and still cause a response in the nervous system. Simple acupuncture can be performed with added electrical stimulation where the impulse is provided directly on the needle through an electric conductor attached to the external cable of the needle. Moxibustion can be also an adjuvant method where heat is applied directly on TCM-designated acupoints. Other forms of actions...
on the acupoints can be done by laser stream instead of through the classical needle insertion. The auricular acupuncture is described as a microsystem within Chinese medicine, based exclusively on the use of needle insertion in the auricular pavilion.

There are forms of acupuncture that will be considered as exclusion criteria for our systematic review; these are bee venom acupuncture (injection of this substance in acupoints), transcutaneous electrical nerve stimulator, TuiNa (Chinese massage therapy) and mesotherapy (subcutaneous injection of chemical and biological compounds).

The acupuncture in RA can decrease the pro-inflammatory cytokines Interleukin 1 and interleukin 6 and increase the inhibitory cytokines interleukin 4 and interleukin 10; inhibit the function of synovial mast cells and upregulate plasma adrenocorticotropic hormone; downregulate serum cortisol levels and synovial nuclear factor-κB/p 65 immune-activity; and restore the hypothalamus-pituitary-adrenal axis. By stimulating the nervous system, acupuncture may lead to the release of endorphins and other neurohumoral factors, changes in the processing of pain in the brain and spinal cord, as well as an increase in local microcirculation that helps in the dispersal of swelling.

The main reason for pain is assumed to be a systemic inflammation, although psychosocial factors, and peripheral and central pain processing mechanisms, such as loss of descending analgesic activity and central pain augmentation or sensitization, are intricately intertwined. Left untreated RA leads to joint destruction and severe disability. The main features of RA are acute and chronic rheumatic pain, physical function (PF) limitation and a significant impact on health-related quality of life (HRQoL). This systematic review will provide a detailed summary of the current state of scientific evidence based on the effects of acupuncture for pain relief as well as PF and HRQoL improvement in patients with RA.

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage. However, pain is more than a sensation; the physical awareness of pain also includes perception, the subjective interpretation of the discomfort.

Acute pain is the body’s normal response to damage such as a cut, an infection or other physical injuries. It is often sudden in onset, as it is usually the direct result of a noxious stimulus. It often goes away in a few weeks or months if treated properly. Acute pain can become chronic when the cause is difficult to treat.

Chronic pain is, by definition, present for at least three months. It can be affected by physical, environmental and psychological factors. Chronic pain often cannot be treated or cured; it can only be managed. Chronic pain may persist because the original inciting stimulus is still present and/or because changes to the nervous system have occurred, making it more sensitive to pain. Therefore, chronic pain in RA may reduce QoL, wellbeing and the ability to function over the long term.

According to TCM, the meridian system or neurovascular network per se can conduct and transmit nerve signals irrespective of whether it is pain or not. In the case of RA, stagnation in the joints will produce arthritis pain but if the stagnation or blockage of the neurovascular flow in that part of the body is removed, then the pain syndrome will also disappear.

Pain relief can be achieved by acupuncture through adjusting the impedances of the meridian system, which is connected internally with viscera and externally with limbs and sensory organs. Initially, the injury around the acupoint is produced, then the magneto-electric inductive effects along the meridian system will be triggered, and finally the analgesia/pain relief can be obtained via the impedance matching/mismatching with the pain source brain.

The negative consequences of RA on the PF of patients are multidimensional, involving decrease in muscle strength and endurance and restricted range of joint movement.

The PF domain is theoretically composed of four subdomains that are conceptually related but distinct: mobility (lower extremity), dexterity (upper extremity), axial or central (neck and back function) and complex activities that involve more than one
subdomain (instrumental activities of daily living). In practice, the subdomain assignment may sometimes be arbitrary, as many tasks involve more than one part of the body. Physical function scales are used in the majority of clinical trials to assess the effectiveness of treatment and have become established instruments for assessing health outcomes in clinical practice and observational studies as well.

Consequently, PF is a key component of patient-reported outcome assessment in rheumatology and includes specific tasks being evaluated in a standardized manner using predetermined criteria such as time, number of repetitions, force and degree of movement.

Patients with RA have body pain, fatigue, substantially lower mental HRQoL, and reduced levels of PF, levels of vitality, social functioning and global health in comparison with other health conditions.

Quality of life is a ubiquitous and multidimensional concept that has different philosophical, political and health-related definitions. Health-related QoL self-reports comprise physical, functional, social and emotional wellbeing, as well as the biological integrity of individuals.

Measurement of HRQoL is supported by the National Institute for Health and Care Excellence guidelines and is potentially useful for several reasons. Many patients value HRQoL more than disease-related variables such as inflammatory biomarkers or joint counts; reduced HRQoL in RA patients is associated with increased use of healthcare resources and levels of depression.

With the aim of determining the efficacy of acupuncture for pain relief in patients with RA, Wang et al. conducted a systematic review. They concluded that questionable evidence exists in placebo-controlled trials concerning the efficacy of acupuncture for RA.

The systematic review conducted by Lee et al. concluded that the evidence on the effects of acupuncture to treat RA was not convincing. The number, size and quality of the randomized controlled trials were too low to draw firm conclusions.

These systematic reviews showed methodologic concerns and questionable conclusions regarding the effects of acupuncture in the treatment of RA. The evidence is limited due to methodological considerations, such as type of acupuncture, site of intervention, sample size, long-term benefits that remain unknown, inappropriate randomized-control or blind interventions, and scarce use of validated outcome measures. Our systematic review will be based on previous published studies and therefore will comprise the same limitations.

However, acupuncture is often advocated for the treatment of RA. A systematic review comparing different therapies to treat rheumatic diseases including RA showed that acupuncture was the therapy that had the most significant evidence.

To understand the specific evidence of the potential benefits or possible impairment of acupuncture on the HRQoL in RA, a thorough search was conducted in several databases (Prospero, CINAHL, Medline, Cochrane, JBI Database of Systematic Reviews and Implementation Report). Relatively few rigorous clinical trials have been published, the recent scientific evidence is scarce and the most recent systematic review for this topic is over five years old.

This review will benefit patients and practitioners and lead to new requirements in the field of traditional and complementary medicine therapies.

Inclusion criteria
Types of participants
The review will consider studies that include patients (regardless of gender, age, race and ethnicity) suffering from RA classified according to the American College of Rheumatology.

Type(s) of intervention(s)
The review will consider all studies regarding patients with RA who have been treated with needle acupuncture with or without electrical stimulation, laser at precise locations for the purpose of therapy, auricular acupuncture, or moxibustion on the body as the sole treatment or as an adjunct to other treatments. Animal trials will be excluded.

The trials of acupuncture that exclude patients being submitted to western therapy or wherever only immunological or biological parameters are assessed will be excluded.

Comparator
In our review we will include trials comparing acupuncture with placebo or sham acupuncture as also acupuncture versus conventional western treatments. Studies will be excluded if they compare the use of TCM acupoints with transcutaneous electrical nerve stimulator, bee venom acupuncture,
TuiNa or mesotherapy but are not really using any of the acupuncture techniques.

When acupuncture is used as a complementary therapy it is expected that the control group has received the same conventional treatment as the acupuncture group.

**Outcomes**

This review will consider studies that include the following outcome measures:

**Primary outcomes**

- Health-related quality of life (HRQoL)
  - Measurement tools:\n    - 36-item Short-Form Health Survey (SF-36)
    - Arthritis Impact Measurement Scales
    - Health Assessment Questionnaire Disability Index
    - Health Assessment Questionnaire (HAQ)
    - Rheumatoid Arthritis Quality of Life (RAQoL)
- Pain measurement instrument (RAQoL)
  - Measurement tools:
    - Visual Analogue Scale (VAS)
    - Numeric scale
    - Faces Scale
    - Qualitative Scale.
- Physical function (PF)
  - Measurement tools:\n    - Item Response Theory
    - Visual Analogue Scale and Computerized Adaptive Testing
    - Disease-specific HAQ
    - Groningen Activity Restriction Scale (GARS)
    - McMaster Health Index Questionnaire (MHIQ).

**Secondary outcomes**

- Symptom (morning stiffness and functional impairment) following the ACR criteria.
  - Measurement by its duration to maximum improvement and by its severity on a VAS.
- The number of joints affected by RA, assessed by a tender joint count.
- Serum concentrations of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein level, cortisol, interleukins, anti-citrullinated protein antibodies and rheumatoid factor.
- Adverse effects.
- Autonomy.
- Measurement by self-reported survey directly or indirectly in the survey defined by other outcomes, for example, HRQoL.

**Types of studies**

The review will consider experimental study designs, including randomized controlled trials, non-randomized controlled trials, quasi-experimental and before and after studies.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English, Portuguese, German and Chinese will be considered for inclusion in this review. Studies published from databases inception up to 2015 will be considered for inclusion in this review.

Dissertations and abstracts will be included if they contain sufficient detail.

The searched databases will be:

- Medline
- Cochrane Central Register of Controlled Trials (CENTRAL)
- AMED
- British Nursing Index
- CINAHL
- China Academic Journal
- Century Journal Project
- China Doctor/Master Dissertation Full Text DB
- China Proceedings Conference Full Text DB
- Proquest
- RCAAP
- Open Grey

Initial keywords to be used will be: acupuncture, rheumatoid arthritis, quality of life, pain, functional impairment, physical function, randomized controlled clinical trial.
**Assessment of methodological quality**

Quantitative articles selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Patient blinding will be assumed in cases where the control intervention is indistinguishable from acupuncture, even if the word “blinding” did not occur in the report.

**Data extraction**

Quantitative data will be extracted from articles included in the review, by two independent reviewers, using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

To find any missing data, the authors of included primary studies will be contacted.

**Data synthesis**

Quantitative articles will, if possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subjected to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences or standardized mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis.

Heterogeneity will be assessed statistically using the standard \( \chi^2 \) and also explored using subgroup analyses based on the different quantitative study designs included in this review.

If the data is available, we will conduct subgroup analyses to explore the heterogeneity between the studies. Subgroups will include the following:

- Type of acupuncture:
  - Acupuncture or acupuncture plus moxibustion versus conventional drugs
  - Type of control
  - Duration of RA
  - Laterality of RA – bilateral RA versus unilateral RA.

Wherever statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation, if necessary.

**Acknowledgements**

The authors thank the support provided by Health Sciences Research Unit: Nursing (UICSA: E), hosted by the Nursing School of Coimbra (ESEnfC).

**References**


8. He TF, Yang WI, Zhang SH, Zhang CY, Li LB, Chen YF. Electroacupuncture inhibits inflammation reaction by upregulating vasoactive intestinal peptide in rats with adjuvant-
Appendix I: Appraisal instruments

**MAStARI appraisal instrument**

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
<td>☐</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
<td>☐</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
<td>☐</td>
<td>☐</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
<td>☐</td>
<td>☐</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

______________________________________________________________________________
Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer ___________________________ Date ___________________________
Author ___________________________ Year ___________________________
Journal ___________________________ Record Number ___________________________

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐
Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A ___________________________ Group B ___________________________

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:
### Study Results

#### Dichotomous Data

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#### Continuous Data

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