

Effect of acupuncture therapy on regulating serum cytokines : a systematic review and meta-analysis protocol

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Protocol

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Abstract

Introduction: There is still a lack of evidence-based, safe, and high benefit/harm ratio full-term prevention and treatment methods to effectively inhibit the release of the inflammatory factors. Serum cytokine level indicates the severity of inflammatory activities in surgery, infection, and many diseases. Accumulating evidence has shown that acupuncture, which has the advantages of safety, simplicity, and low price, can reduce serum cytokine levels.

Methods and analysis: We will search three English databases (PubMed, EMBASE and Cochrane Library) and four Chinese databases (Chinese biomedical literature database, VIP database for Chinese technical periods, China National Knowledge Infrastructure, and Wanfang) to obtain all RCT studies. Research of other types will not be included. But no literature will be excluded due to the publication date. Two independent reviewers will conduct research screening of three levels (title, abstract and full text), data extraction and bias risk assessment according to the inclusion/exclusion criteria, and their differences will be resolved by a senior researcher. Random or fixed-effect models will be used according to data heterogeneity. The data will be expressed as the risk ratio of binary data or the average difference of continuous data, and the confidence interval (CI) of all results is 95%.

Ethics and dissemination: Since only the data in the published literature are used for secondary analysis, there is no need to re-apply for ethical review. We will publish the results of this study and share the findings with our peers at international conferences.

PROSPERO registration title and number: Effect of acupuncture therapy on regulating serum cytokines: a systematic review and meta-analysis

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Introduction

Surgery, infection, or chronic diseases damage tissues and trigger intense immune activities, resulting in the production and release of cytokines [1]. Such immune activities often aggravate the subsequent infection, pain, immune injury, and tumor progression [2–3], which contributes to the progress of many diseases to emergency and critical stage. The accumulation of inflammatory factors, the material basis for excessive immune activities, can cause cytokine release syndrome (CRS), which is also named cytokine storm syndromes(CSS). In CRS, a variety of immune cells undergo recruitment and chemotaxis, resulting in local severe oxidative stress injury and pathological product accumulation, which directly accelerate disease progression [4].

For example, in COVID-19, the accumulation of inflammatory factors leads to massive exudation of airway secretions (including many inflammatory cells and inflammatory secretions), pulmonary interstitial edema and bleeding, which are key contributors to acute respiratory distress syndrome (ARDS) [5–6]. Another example is that in the progression of chronic diseases, such as coronary atherosclerosis,

the increase of serum inflammatory level makes the plaque unstable, which can contribute to the occurrence of adverse cardiovascular events [7]. Although inflammatory factors mainly play a role in local lesions through autocrine and paracrine mechanisms [8], the level of serum inflammatory factors can reflect the local and even the overall severity of inflammation, indicating the degree of disease progression.

In general, excessive serum cytokines are harmful to human body. Steroids and antihistamines can be used for the treatment of circulating cytokines, but they have some side effects and can only be applied under relatively strict conditions. Therefore, they are considered when the clinical benefits far outweigh the side effects. Though monoclonal antibody products are potential alternative treatment for excessive cytokines, they are still in the pre-market or initial stage [9–10]. They are also expensive, with strict indications and strong therapeutic specificity. Hence, monoclonal antibody products are not suitable adjuvant drugs for general diseases. Currently, there is still a lack of evidence-based, safe, high benefit ratio, and full-term prevention and treatment methods to effectively reduce these inflammatory factors [11].

In recent years, the clinical research on non-drug supplements and substitution therapy in traditional Chinese medicine is burgeoning [12]. More and more studies show that in addition to alleviating the clinical symptoms and improving the quality of life of patients, acupuncture treatment can reduce the level of serum pro-inflammatory factors in a variety of diseases [13–15]. Importantly, as an in-vitro treatment method, acupuncture has the advantages of less toxicity and side effects, low cost, minimal impact on liver and kidney function, and good compliance [16], being a promising full-term and general intervention. In fact, acupuncture, having been used in China for more than two thousand years, is now recognized in many countries. Evidence has shown that various derivative therapies, such as electroacupuncture and acupressure, are effective in pain relief and improvement of postoperative urinary retention [17–18].

In the existing studies, for many diseases treated with acupuncture, the level of serum inflammation is often included as an accompanying index to evidence the effect of acupuncture. But the quality of this evidence is not uniform and the conclusions are inconsistent [19]. In this study, we will sort out and review the existing literature to obtain more reliable evidence for the effect of acupuncture on serum cytokine level.

Objective

Systematic review and meta-analysis (if applicable) will be conducted to explore whether acupuncture treatment can significantly reduce the serum cytokine level in adult patients compared with the non-acupuncture and sham acupuncture (acupuncture at random spots on the skin) groups (see search strategy for details). Our goal is to obtain conclusive evidence of the effect of acupuncture on relieving inflammation.

Methods

Overview

This research scheme has been registered and reviewed on the international prospective register of systematic reviews (PROSPERO). We will prepare this scheme according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement [20]. A detailed explanation document will be used as an assist guidance [21]. We will further proceed with the work according to the worklist of PRISMA [22].

Eligibility criteria

In this study, we will extract the information from the original studies, including PICO, study design, grouping, and time frame. We will record the year, language, publication status and type of the study.

Study design

All the clinical randomized controlled trials(RCT) involving the effect of acupuncture therapy on serum cytokines will be considered according to the inclusion and exclusion criteria in the review.

Participants

To obtain the results of a large-scale sample, this study will involve all adults(over 18 years old) regardless of race, age, gender or comorbidity in the original studies. Besides, this work will not limit the disease or condition types (whether acute or chronic diseases or surgery).

Interventions

Any observation and comparison of serum inflammatory factors before and after acupuncture treatment(including normal acupuncture and electroacupuncture) will be included in this study. It is worth noting that acupuncture intervention must serve as treatment, so studies involving acupuncture for anesthesia or cosmetic purposes will not be included.

Outcomes

Primary Outcomes. Major serum cytokines: chemokines, interferons, interleukins, lymphokines, monokines, tumor necrosis factors.

Secondary Outcomes. Pain score, quality of life score, serum C-reactive protein level, improvement of primary diseases and side effects.

Language

We will include articles reported in the English and Chinese. Possibly relevant studies in other languages will be displayed in an list.

Information sources and search strategy

We will search three English databases (PubMed, EMBASE and Cochrane Library) and four Chinese databases (Chinese biomedical literature database, VIP database for Chinese technical periods, China National Knowledge Infrastructure, and Wanfang). An example of the search protocol in PubMed is attached in the supporting materials (supplemental table 1). We will also review the references of the retrieved literature to further screen the studies that meet the inclusion criteria. We will manage to include more grey literature by contacting the authors according to their information on the trials' registration websites (clinicaltrials and Chinese clinical trial registry). Duplicate data and studies will be strictly excluded.

Study selection

In order to obtain eligible literature, we will import the titles and abstracts of all literature obtained according to the retrieval strategy into Endnote software (Version X9). After eliminating duplicate literature, two researchers will independently screen the literature based on the title, abstract and full text according to the inclusion criteria and exclusion criteria. After the screening work is completed, all controversies will be resolved by another researcher.

Data extraction and synthesis

Two researchers will independently extract data from the included literature by using the specific software Review Manager Version 5.4 (The Cochrane Collaboration, 2020) according to the requirements of PRISMA to reduce possible bias. The controversies will be finally resolved by a third researcher. Considering that we do not limit the time span, we will not contact the original author to further confirm the small amount of missing or unclear data. The extracted data are supposed to include the following information:

General information: title, first author, correspondence information, funding, publishing year, publisher.

Participants: age, nationality, race, gender, treatment purpose (disease or surgery), duration of suffering.

Intervention: treatment type, treatment period, treatment frequency, combined drugs, other details.

Outcomes: Primary outcomes (primary cytokines in peripheral circulating blood: Chemokines, Interferons, Interleukins, Lymphokines, Monokines, Tumor Necrosis Factors). Secondary outcomes. Pain scores, quality of life score, serum C-reactive protein, improvement of primary diseases and side effects. (if exist).

After data extraction, we will synthesize the data by quantitative or qualitative comparison. Based on our primary investigation, a quantitative analysis is going to be executed.

Assessment of heterogeneity and publication bias

Since this analysis is expected to include multiple studies, different evaluation methods may be used. We will evaluate the heterogeneity of these studies by using the I^2 test. An I^2 test value higher than 50% is considered to indicate heterogeneity. Otherwise, it is considered that there is no heterogeneity between these studies. If the literature is heterogeneous, we will re-examine the original data in the literature, and conduct subgroup analysis, regression analysis, and sensitivity analysis to identify the source of heterogeneity.

If the source of heterogeneity cannot be determined, we will change to descriptive statistics.

Based on the nature and quantity of data, we will show the publication bias of the included literature in the form of forest charts and funnel charts.

Assessment of certainty of evidence

To evaluate the quality of these studies, we will follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach by using GRADE profiler software Version 3.6 (McMaster University, ON, Canada). Finally, a summary-of-finding list will be generated by the software to rank the candidate studies based on the indirectness, inconsistency, imprecision, and risk of publication bias of the review results.

Discussion

Although the pathological changes of diseases are different, the essence of inflammatory response is consistent under the action of pathogenic factors. A large number of studies have shown that acupuncture therapy can reduce the level of serum inflammation in distinct illnesses, however, there are also a few studies that do not show the effect. In such context, we plan to systematically compare the effect of acupuncture therapy to of non-treatment or sham acupuncture groups on regulating the serum cytokines level. To the best of our knowledge, this is the first systematic review and meta-analysis of whether inflammation can improve disease-related cytokines releasing in serum. This result can guide clinicians to more confidently choose acupuncture as an alternative anti-inflammatory strategy in multiple clinical conditions.

Declarations

Patient and public involvement

No patient will be directly involved in the design or conception of this study.

Ethics and dissemination

This study will only use the data in the published literature for secondary analysis, so there is no need to reapply for ethical review. We will publicly publish the results of this study and share the findings with our peers at international conferences.

Authors' contributions

PL is the guarantor. PL and XTF proposed the conception of the study. This manuscript protocol was drafted by XTF and was revised by PL. The selection criteria, data extraction methods and the risk of bias assessment strategy were designed by YFZ and YRW and developed by all the authors. MD and SJL designed the search strategy. JD and JRW provided statistical expertise. PL contributed to expertise on acupuncture and inflammation. All the co-authors have read this manuscript, provided feedback and approved the publication of this final protocol.

Consent for publication

Neither the entire manuscript nor any part of it has been published or submitted to other journals. All the authors agree to publish this manuscript on this journal.

Competing interests

No competing financial interests exist for all the authors.

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Figures

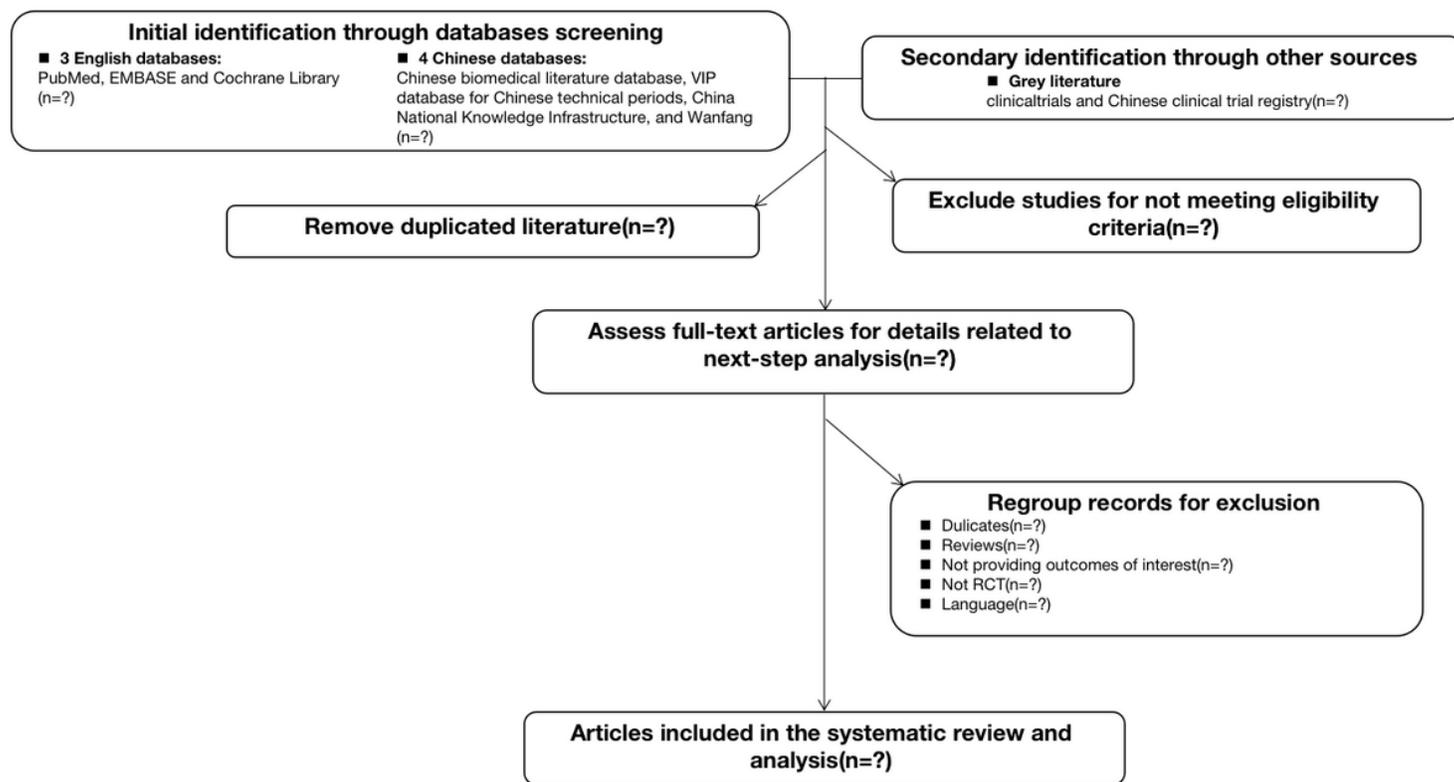


Figure 1

Flowchart

Supplementary Files

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- [PRISMAP2015checklist.docx](#)
- [supplementmaterialOnlineSearchstrategy.pdf](#)