Efficacy of acupuncture in improving the symptoms and life quality of patients with moderate or severe acne vulgaris: protocol for a randomized controlled trial

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Abstract

Background: Acne vulgaris (AV) is a common chronic dermatologic disease that tends to impair the appearance and quality of life (QoL) of patients. Although acupuncture has been indicated as an effective treatment for patients with AV in several trials, the results of these trials are also controversial due to potential for bias of their design. And none of the previous clinical trials of acupuncture therapy for AV used the QoL as a primary outcome or employed a sham acupuncture control arm. The aim of the study is to evaluate the effect of acupuncture on the symptoms and QoL of patients with moderate or severe AV.

Methods/design: Ninety-six eligible participants with AV will be randomly assigned to acupuncture or sham acupuncture groups (1:1 allocation). All participants will receive 4-week treatment comprising of a total of 12 sessions (3 sessions per week). The primary outcome will be change from baseline in the Skindex-16 scale total score at treatment completion. The secondary outcomes will be Skindex-16 subscale scores, the Dermatology Life Quality Index scale total score, the total lesion count and inflammatory lesion count, itch and pain assessment using the visual analogue scale score, patient expectations of acupuncture, and the blinding of the effect of sham acupuncture. Follow-up evaluation will be performed at weeks 16 and 28. All outcome analyses will be performed in the intention-to-treat population.

Discussion: We expect to evaluate the effectiveness of acupuncture on the symptoms and QoL of patients with moderate or severe AV compared with sham acupuncture. The limitation of the design of this trial is that the single center study with a relatively small sample size, the acupuncturists will not be blinded.

Background

Acne vulgaris (AV) is a common chronic dermatologic disease involving pilosebaceous units [1, 2]. Skin lesions, as one of the common symptoms of AV, typically appears at the areas of face, chest and back [1, 3]. An estimated 79–95% of adolescent population is affected by it [4]. It may present as comedones, erythematous papules, pustules, nodules, deep pustules, and scarring. The occurrence of AV lesions on face may induce anxiety and lowered self-esteem [5, 6], thus leading to a decline in the
quality of life (QoL) \cite{5-8}.

The American Society of Dermatology recommends benzoyl peroxide, topical retinoids, or systemic antibiotic therapy as the first-line treatment for mild to severe AV \cite{1-3}. However, these pharmaceutical therapy may cause side effects of drying, peeling, erythema, skin irritation, and long-term treatment period may result in drug resistance and recurrence rate is relatively high \cite{9}. For those reason, there is an increasing interest in seeking help from natural and safer therapies \cite{9, 10}. These natural and safer treatments include complementary and alternative treatment remedies, such as herbal medicine and acupuncture \cite{9, 10}.

Several trials have indicated that acupuncture may alleviate the skin lesions and improve the QoL of patients with AV \cite{11-15}. However, these trials were of potential bias due to small sample sizes, non-placebo/sham/waiting list control or using self-defined outcome assessment, thus making it difficult to evaluate the efficacy of acupuncture on AV patients. So we have conducted a pilot trial (unpublished) from April 2017 to March 2018, 42 patients with moderate or severe AV were randomized into acupuncture group (n = 21) or sham acupuncture (n = 21) group. After 4-week treatment, the reduction in the number of skin lesions in acupuncture and sham acupuncture was \(-6.62 \pm 15.42\) and \(-15.10 \pm 20.13\), without significant difference (P = 0.137), which contradicts the results of previous trials \cite{11-14}. On the contrary, after 4-week treatment, the reduction of Skindex–16 scale total score in acupuncture and sham acupuncture was \(-12.50 \pm 19.09\) (32.39 \pm 21.36 at baseline and 19.89 \pm 15.40 after treatment) and \(0.40 \pm 21.12\) (30.03 \pm 20.78 at baseline and 30.43 \pm 19.39 after treatment), with a significant between-group difference (P = 0.044). Results of our pilot study indicated that acupuncture may relieve symptoms and improve QoL of patients with moderate or severe AV. And there are several randomized controlled trials on the efficacy of positive drugs (such as isotretinoin and or antibiotics) in improving on AV and their effects on QoL have been conducted in recent years \cite{16-17}. Therefore, we plan to conduct this study to evaluate the effect of acupuncture on the symptoms and quality of life of patients with moderate or severe AV, compared with sham
Methods/design

Study design

The proposed study is a prospective, randomized, sham acupuncture controlled trial with two parallel arms using a 1:1 allocation ratio. The trial will be conducted at the Guang’anmen Hospital, China Academy of Chinese Medical Sciences. The study protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [18] and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [19].

Study recruitment

Participants will be recruited between August 2019 and August 2020 at Guang’anmen Hospital via advertisements, posters, Wechat, and hospital websites. The screening and recruiting process will be completed by research assistant. The diagnosis, classification, and differentiating inflammatory AV will be undertaken by dermatologist. All information, including demographic and clinical characteristics of participants at baseline will be recorded by research assistant.

Randomization and allocation concealment

The randomized scheme has been prepared by the National Clinical Drug Testing Institute of Guang’anmen Hospital. Participants will be randomly assigned to receive acupuncture or sham acupuncture treatment in 1:1 ratio with the fixed block of four. Sealed opaque envelope will be used to ensure randomization concealment. The number of randomization sequence and information of group allocation will be sealed in ordered envelopes. With the inclusion of patients, those envelopes will be opened one by one in sequence. The envelopes will be kept by a researcher assistant who is not involved in the treatment or assessment. Additionally, all participants will undergo a baseline assessment (~1 week to 0 week) prior to randomization by the assistant researchers.

Blinding

The participants, outcome assessors, and statisticians will be blinded to the group allocation. However, because of the characteristics of acupuncture, acupuncturists will not be blinded in this trial. To assess the blinding effect of sham acupuncture, participants will be asked to answer the
following questions within 5 minutes after any treatment in week 4: “Do you think you have received traditional acupuncture?” The response options will be “Yes,” “No,” or “Unclear.”.

All participants will sign informed consent before enrolment, and are allowed to withdraw at any time during the course of this study. The process of the study is shown in Figure 1.

**Ethical approval**

This clinical trial will adhere to the principles of the Declaration of Helsinki, and has been approved by the Ethics Committee of the Guang’anmen Hospital (2018-137-KY-01) (See Additional file 1).

**Participants**

Ninety-six eligible participants with AV will be recruited in the trial.

**Inclusion criteria**

Individuals aged between 18 and 48 years old who meeting the diagnostic criteria for AV [20, 21]; Scoring between 19 and 38 by Global acne grading system (GAGS) score [22].

**Exclusion criteria**

Participants with any of the condition below will be excluded:

- Individuals with polymerization acne, explosive acne, drug acne, premenstrual acne, cosmetic acne, occupational acne, or any other subtypes of acne;
- Individuals with other severe diseases that may affect the acne, such as polycystic ovary syndrome, thyroid disease, or atypical congenital adrenal hyperplasia;
- Individuals with other skin diseases that may influence the assessment of AV, such as rosacea, folliculitis, or other skin diseases;
- Individuals who have received antibiotics, retinoic acid, steroids, or anti-inflammatory drugs in the past month;
- Individuals with severe heart, liver, kidney, hematopoietic system or autoimmune disorders, or severe systemic malnutrition;
- Pregnant and lactating women or those planning to conceive within 12 months;
- Individuals who have received acupuncture treatment in the past 3 months.

**Intervention**

All participants will receive treatment for 4 weeks with 3 sessions per week (ideally every other day), for a total of 12 sessions. Acupuncturists with undergraduate degree or above and clinical experience over 1 year at the Guang’anmen Hospital will be responsible for treatment. Participants will be treated separately to avoid communication during the trial period. We will discourage all included participants to receive any other treatment for AV during study. If participants received any other treatment for AV, they will also be included in this study and all details of another treatment for AV
will be record in case report form. We will compare the proportion of participants using other treatments between groups.

**Acupuncture group**

The locations of acupoints is described as per ‘the Nomenclature and Location of Acupuncture Points (National Standard of People’s Republic of China, 2006 [GB/T 12346-2006])’ \(^{[23]}\). The selections of acupoints will be decided with reference to the ‘Guidelines for AV treatment in China’ (revised version 2014) \(^{[24]}\). Participants in acupuncture group will receive stimulation at Dazhui (CV14), bilateral Quchi (LI11), bilateral Hegu (LI4), bilateral Zusanli (ST36), and bilateral Neiting (ST44) with disposable acupuncture needles (0.30×40 mm, Huatuo Brand, Suzhou Medical Appliance, China). After routine disinfection, acupuncture needles will be inserted obliquely into CV14 to a depth of 30–40 mm at an angle of 15°–30°; acupuncture needles will be vertically inserted into bilateral LI11, bilateral LI4, bilateral ST36, and bilateral ST44 to a depth of 25–30 mm for 3 times (once every 10 minutes) with slight lifting, thrusting, and twisting manipulations to produce a sensation of de-qi. Each session of acupuncture will last for 30 minutes.

**Sham acupuncture group**

Participants in sham acupuncture group will receive sham acupuncture at sham CV14 (10 mm to CV14), LI11 (10 mm to LI11), LI4 (10 mm to LI4), ST36 (25 mm to ST36) and ST44 (10 mm to ST44) with disposable acupuncture needles (0.30×25 mm, Huatuo Brand, Suzhou Medical Appliance, China). Sham CV14, LI11, LI4, ST36, ST44 will be vertically inserted to a depth of 1–2 mm without any manipulation and de-qi. The treatment sessions will last for 30 minutes.

Participants will not be allowed use of other treatments for AV throughout the trial. Detailed information pertaining to use of other treatments will be recorded in the case report form.

**Rescue medication**

Participants will not be encouraged to receive other treatment or medication during the study in case of influence to the results. However, if the condition of AV deteriorates during 4-week treatment and 24-week follow-up, mincycline orally-taken hydrochloride capusules will be given to the patient,
100mg per daily for 7 days, to relieve the symptoms of pain or itching of skin. Details of medication used will be recorded in the case report form. We will compare the proportion of participants using rescue drugs between groups.

**Outcome measures**

The primary outcome will be the total score change of Skindex–16 scale from baseline at the end of 4-week treatment. The Skindex–16 scale is a brief, skin-related, quality-of-life scales with satisfactory reliability and validity. It is used to evaluate the efficacy of acupuncture in improving QoL of patients with AV⁻²³,²⁴. The scale includes a total of 16 items which are categorized into three domains: the symptoms of participants with AV, the emotions of participants with AV, and function of participants with AV⁻²⁵,²⁶. The Skindex–16 scale score ranges from 0 (best) to 100 (worst) with the minimal clinically important difference (MCID) as 10⁻²⁵,²⁶.

Secondary outcomes includes:

- The change from baseline in the Skindex–16 scale total score at weeks 16 and 28;
- The change from baseline in the Skindex–16 subscale (the symptoms of participants with AV, the emotions of participants with AV, and functioning of participants with AV) scores at weeks 4, 16, and 28;
- The change from baseline in the Dermatology Life Quality Index (DLQI)⁻²⁷ scale total score at weeks 16 and 28. DLQI scale is a tool to assess health-related QoL of patients with skin diseases. It has a total of 10 items. The total score of DLQI ranges from 0 (best) to 100 (worst) with 10 as the MCID⁻²⁸. The change from baseline in the total lesion (inflammatory and non-inflammatory lesions) counts (TLC)⁻²⁹,³⁰ at weeks 4, 16 and 28;
- The change from baseline in the inflammatory lesions counts (ILC)⁻³¹ at weeks 4, 16 and 28. The inflammatory lesions include the inflammatory papules, pustules, and cysts. The non-inflammatory lesions include the black and white head comedones. The lesions are assessed on the forehead, cheeks, nose, and chin. The inflammatory and non-inflammatory lesions are counted from the face pictures obtained using a digital camera by a dermatologist.
- The change from baseline in the degree of itch assessed by visual analogue scale (IVAS)⁻³⁰ at weeks 4, 16 and 28;
- The change from baseline in the severity of pain assessed by visual analogue scale (PVAS)⁻³² at weeks 4, 16 and 28;
- The participants’ expectations of acupuncture will be assessed at baseline using the following 2 questions: “Do you think acupuncture will be effective for treating the illness?” and “Do you think acupuncture will be effective for relieving the related symptoms of AV?” The response options will be “Yes,” “No,” or “Unclear.”.

The details of the evaluation of outcomes are shown in Table 1.

**Safety evaluation and blinding assessment**
Adverse events (AE) including AEs related to acupuncture (broken needle, local hematoma, infection, abscess, and others), AEs related to post-acupuncture (nausea, vomiting, palpitations, dizziness, headache, insomnia, or any other symptoms after acupuncture treatment), and AEs unrelated to treatment. For safety assessment, details of all AEs will be recorded in the case report form by a research assistant. Any serious adverse events (SAEs) will be reported to the Ethics Approval of Guang’anmen Hospital of China Academy of Chinese Medical Sciences of within 24 hours. The department of Acupuncture of Guang’anmen Hospital of China has insurance to compensate the injure related to the interventions during this study.

**Sample size and statistical analysis**

The sample size of this trial was calculated based on the primary outcome, which is the change from baseline in the Skindex–16 scale score at the end of week 4. In our unpublished pilot trial, the mean (± standard deviation) reduction in the Skindex–16 scale score after 4-week treatment was -12.50 ± 19.09 and 0.40 ± 21.12 after treatment for the acupuncture and the sham acupuncture groups, respectively. Assuming an alpha risk of 5% and a beta risk of 20%, a sample size of 96 (48 participants in each group) was calculated considering a 20% dropout rate.

The data will be analyzed using SPSS software V.20.0 (IBM SPSS Statistics; IBM Corp, Somers, NY) according to intention-to-treat principle. Normally distributed continuous variables will be reported as mean± standard deviation and 95% confidence intervals; non-normally distributed continuous variables will be reported as median (interquartile range). Categorical variables will be presented as frequency (%). For data pertaining to drop-outs, multiple imputation will be used for statistical analysis. Between-group differences with respect to normally distributed continuous variables will be assessed using the ANCOVA or Chi-squared test; those with respect to non-normally distributed continuous variables will be assessed using the non-parametric Wilcoxon statistics. Chi-squared test will be used for categorical variables. All P values will be two-tailed; P ≤ 0.05 will be considered indicative of statistical significance.

**Quality control**

All researchers will receive a training course before the beginning of this trial. Due measures will be
implemented to ensure the traceability and confidentiality of the case report form, informed consent form, and other original data. Double input method will be used for data entry. AEs will be recorded in detail, properly handled, and tracked. All trial-related procedures and data management will be supervised. The Data Monitoring Committee of Guang’anmen Hospital will regularly monitor the recruitment and screening of participants, data collection, monitoring and verification of AEs to ensure the study conducted in accordance with this protocol.

Discussion
AV is a common chronic inflammatory dermatologic disease. It may affect the physical and mental health of patients, and reduce their QoL [33]. An epidemiology study presented that around 20% of young people are influenced by moderate-to-severe AV [34]. It is also reported by some studies that the QoL is correlated with the severity of dermatologic disease [35, 36]. For this reason, this study will only include participants with moderate or severe AV. The primary outcome of the study will be measured by the skindex–16 scale. It is a validated and sensitive scale to measure the QoL of patients with dermatologic diseases [25, 26]. As lesions of AV mainly occur on the area of face and accompany with other symptoms of itch and pain [30, 32], patients tend to present with psychosocial symptoms and reduced QoL. Skindex–16 scale consist of 16 questions in symptoms, emotion and function domains, with each question measured by seven-point Liker scale [26, 37]. And this scale include 7 questions related to the symptoms (itch or pain) and characteristics (lesions) of AV. It is sensitive and specificity to the symptoms and QoL of patients with moderate or severe AV. Moreover, we also used the DLQI scale to evaluate the QoL. It is a brief, skin-related, quality-of-life scales with satisfactory reliability and validity to further evaluate the efficacy of acupuncture in improving the quality of life of patients with AV [27]. These would further evaluation of the effect of acupuncture on the quality of life. In addition, TLC, ITC, IVAS, and PVAS are also used as secondary outcomes to assess the lesion counts and main symptoms (itch or pain) related to AV. These would provide a comprehensive evaluation of the overall effectiveness of acupuncture. In this trial, we aim to evaluate the therapeutic effect of acupuncture on the symptoms and QoL of
patients with moderate or severe AV. The possible placebo effects of acupuncture include the participants’ expectations of acupuncture, the trust degree of acupuncturist and participant, and any difference of the type, frequency or course of the intervention of acupuncture \cite{38, 39}. To partially exclude the placebo effects and demonstrate the real effect of acupuncture, we plan to use sham acupuncture as comparator. Non-insertion-type needle on non-acupoints was proven to be optimal method to reduce possible biological effects \cite{38, 39}. However, the non-insertion-type needle leaves no marks or wounds on the skin. In this condition, the observation of “no needle marks” by participants may put risk on blindness. Therefore, we will opt for non-acupoints and minimal acupuncture without any manipulation as the sham acupuncture in this trial. Non-acupoints are in proximity to the classical acupoints, which will increase the feasibility of blinding.

However, some limitations of our study should be acknowledged. First, the single center study with a relatively small sample size may lead to overestimation of the effects of acupuncture. Second, because of the characteristics of acupuncture, the acupuncturist will not be blinded in our trial, which may cause potential bias. Lastly, the use of non-acupoints and minimal acupuncture without any manipulation may cause some biological effect leading to false-negative results \cite{38}.

**Trial Status**

No recruitment at the present.

**Abbreviations**

AV = Acne vulgaris, QoL = quality of life, SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, STRICTA = Standards for Reporting Interventions in Clinical Trials of Acupuncture, GAGS = global acne grading system, MCID = minimal clinically important difference, DLQI = Dermatology Life Quality Index, TLC = total lesions counts, ITC = inflammatory lesions counts, IVAS = Itch Assessment with Visual Analogue Scale, PVAS = Pain Assessment with Visual Analogue Scale, AE = Adverse events.

**Declarations**

*Ethics approval and consent to participate:* The study protocol has received approval from the Institutional Review Boards of Guang’anmen Hospital in China (approval 2018–137-KY–01 TEL +86–
10–88001552) (See Additional file 1). All investigators will comply with the Helsinki Declaration. All study participants are voluntarily participated after screening and sign the informed consent. All study participants will have a discussion with the researchers about the procedure, treatment, and possible risks and benefits of the trial. Meanwhile, all study participants will have right to exit test.

*Consent for publication:* Not applicable.

*Availability of data and material:* All of the relevant data will be shared for a period beginning 3 months after publication and ending 5 years after publication.

*Competing interests:* The authors declare that they have no competing interests.

*Authors’ contributions:* Zhishun Liu and Ruimin Jiao conceived the idea of this trial and the design this study. Man Huang and Weina Zhang is responsible for statistical analysis. Ruimin Jiao, Weina Zhang and Man Huang are responsible for the recruitment and treatment of participants. This manuscript was drafted by Ruimin Jiao and revised by Zhishun Liu. All of the authors read and approved the final manuscript.

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Table
Table 1. The time-points for assessment of outcomes
| Measure outcomes                  | Baseline | Week 1 | Week 2 |
|----------------------------------|----------|--------|--------|
| Skindex-16 total score           | ×        |        |        |
| Skindex-16 subscales score       | ×        |        |        |
| DLQI total score                 | ×        |        |        |
| TLC                              | ×        |        |        |
| ILC                              | ×        |        |        |
| IVAS score                       | ×        |        |        |
| PVAS score                       | ×        |        |        |
| Blinding assessment              | ×        |        | ×      |
| Expectation                      | ×        |        | ×      |
| Safety assessment                | ×        | ×      |        |

DLQI, Dermatology Life Quality Index scale; TLC, total lesion count; ILC, inflammatory lesion count; IVAS, itch assessment with visual analogue scale; PVAS, pain assessment with visual analogue scale.

**Figures**

Figure 1

Trial flow diagram

Supplementary Files
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