Acupoint injection of Bacillus Calmette–Guerin polysaccharide nucleic acid for patients with chronic urticaria
A protocol for systematic review

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Abstract

Background: To investigate the efficacy and safety of acupoint injection of Bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN) in the treatment of chronic urticaria (CU).

Methods: The following databases will be searched from their inception: Medline, Embase, Pubmed, Web of Science, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure Database, China Biomedical Literature Database, China Science Journal Database, and Wanfang Database. All databases will be searched from the date of creation until October 2019. In addition, we will manually search the list of medical journals as a supplement. The scope of the search included randomized controlled clinical studies related to acupoint injection of BCG-PSN for CU. The primary outcome is the disease activity control. Secondary outcomes include response rate, adverse events, and recurrence rates. The Cochrane RevMan V5.3 Deviation Assessment Tool will be used to assess bias assessment risk, data integration risk, meta-analysis risk, and subgroup analysis risk (if conditions are met). The average difference, standard mean difference and binary data will be used to represent continuous results.

Results: This study will comprehensively review the existing evidence on the treatment of CU by acupoint injection of BCG-PSN.

Conclusion: This systematic review will provide a judgment basis for the effectiveness and safety of acupoint injection of BCG-PSN in the treatment of CU.

Systematic review registration: PROSPERO, CRD42019139885.

Abbreviations: BCG-PSN = Bacillus Calmette–Guerin polysaccharide nucleic acid, CU = chronic urticaria, MD = mean difference, QOL = quality of life, RCT = randomized controlled clinical trial, SR = systematic review.

Keywords: acupoint, acupoint injection, Bacillus Calmette–Guerin, Bacillus Calmette–Guerin polysaccharide nucleic acid, chronic urticaria, protocol, systematic review

1. Introduction

1.1. Description of the condition

Urticaria is defined as the sudden development of transient hives (wheals) and angioedema or both. A wheal is characterized by a circumscribed superficial edema of the skin, mostly surrounded by bright red erythema and associated with a strong itching or burning sensation. Chronic urticarial (CU) is defined as the presence of urticaria for a period exceeding 6 weeks. Attack twice a week or more. It is divided into chronic inducible urticarias and chronic...
spontaneous urticaria.\textsuperscript{[10]} The etiology of CU is still unknown, but many shreds of evidence suggest that it may be related to different biological systems, such as immunity, inflammation, and coagulation, which causes mast cells and basophils to degranulate and form wheal.\textsuperscript{[4–7]} According to the survey, the global incidence of CU is close to 1%\textsuperscript{[8–11]} It can occur in any age group\textsuperscript{[12]} and has a higher incidence in women than men.\textsuperscript{[9,13–15]} In most cases, symptoms in more than 70% of CU patients will last 2 to 3 years, 20% of them will last more than 3 years. If patients have hypertension, this can be as high as 74%.\textsuperscript{[9,16–18]} 1.8% of CU patients will never recover.\textsuperscript{[19]} Patients have a poor quality of life, with nearly 50% of them suffering from moderate to severe disease activity. CU patients are often accompanied by anxiety, depression, difficulty sleeping, social disorders, and so on, which have a significant impact on the life of CU patients.\textsuperscript{[13,20–23]}

Based on the consensus\textsuperscript{[24,25]} and the guidelines\textsuperscript{[1,26,27]} published between 2014 and 2018, Second-generation H1 antihistamines (sgAH) are the drugs of choice for initial therapy for CU.\textsuperscript{[11]} If unbearable symptoms appear after 2 to 4 weeks or earlier, the dose of the sgAH can be increased to 4 times the manufacturer’s recommended dose (both unlicensed). Omalizumab should be added if it still does not improve significantly. If there is no satisfactory improvement within half a year, it is recommended to use cyclosporine and sgAH for treatment.\textsuperscript{[17,27,28]} The sgAH can improve symptoms, but not reduce the total number of itching wheal episodes.\textsuperscript{[29,30]} Studies have shown that long-term use of antihistamines can cause headaches, drowsiness, fatigue, dry mouth, allergies and other adverse reactions.\textsuperscript{[31–33]} The median tolerance to H1-antihistamines in CU patients was 3 years, and 88.9% of patients had poor CU control.\textsuperscript{[34]} Omalizumab has been shown to be effective,\textsuperscript{[35–37]} but its expensive cost cannot be ignored.\textsuperscript{[38]} Currently, there is no effective treatment for all patients, so it is necessary to explore and evaluate some other treatments to provide more options for the clinical treatment of CU.

1.2. Description of the intervention

Acupuncture is an important part of complementary and alternative medicine. Studies have demonstrated its effectiveness and safety in treating CU.\textsuperscript{[39–41]} Acupoint injection is 1 of the treatments of acupuncture which emerged in China during the 1950s, and it is a modiﬁed acupuncture technique.\textsuperscript{[42]} It originated from intra-muscular injection in western medicine and was gradually integrated into traditional Chinese medicine.\textsuperscript{[43,44]} Acupoint injection is an acupoint-stimulating technique in which a liquid agent is injected to prevent and/or treat diseases.\textsuperscript{[45]} The agents generally include Western medications, Chinese herbal extractions, vitamins, bee venom, and normal saline solution. It is widely used in China for CU\textsuperscript{[42,46,47]} and had good curative effects.\textsuperscript{[48–50]}

Among them, Bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN) is the most commonly used 1 in China.\textsuperscript{[51]} BCG-PSN is 1 of the Immunomodulators which participate in immunomodulatory actions.\textsuperscript{[52]} It is a mixture of nucleic acids and polysaccharides extracted from BCG immune-active substances. Some studies have shown that BCG-PSN can be used in allergic diseases.\textsuperscript{[51,52]} At present, there are many studies on the treatment of CU by injecting BCG-PSN into acupoints in China, and the results were positive.\textsuperscript{[53–56]} But 1 study has reported that BCG-PSN combined with antihistamine did not increase the effect of treating CU.\textsuperscript{[57]} So far, its clinical evidence is insufficient.

From what has been discussed above, The efficacy and safety of acupoint injection of BCG-PSN in the treatment of CU have not been systematically evaluated. Therefore, it is necessary to make treatment recommendations based on the available evidence.

2. Methods and analysis

2.1. Study registration

This Study registration is designed in strict compliance with the preferred reporting items for systematic reviews and meta-analysis protocol.\textsuperscript{[59]} and has been registered at PROSPERO (ID: CRD42019139885).

2.2. Ethics and Dissemination

The results of this systematic review are to evaluate the efficacy and safety of published randomized controlled clinical trial (RCT) about acupoint injections of BCG-PSN for CU to help clinicians and patients choose the appropriate treatment regimen. This review does not require ethical approval and will be reported in peer-reviewed journals.

2.3. Search strategy

We will use computers to search Medline, Embase, Pubmed, Web of Science and Cochrane Central Register of Controlled Trials and China’s four databases: China National Knowledge Infrastructure Database, China Biomedical Literature Database, China Science Journal Database, and Wanfang Database. All databases will be searched from the date of creation until October 2019. The following search terms will be used: Urticaria, CU, Nettle-rash, Hives, Rubella, Wind cluster, Angioedema, acupoint injection, acupoint injection point, acupoint-injection, hydroacupuncture, point injection, acupoint block, BCG, Bacillus Calmette–Guerin, BCG-PSN, BCG polysaccharide nucleic acid, Bacillus Calmette–Guerin polysaccharide nucleic acid, Boolean operators ‘and’ and ‘or’ will be used within the search to combine the search terms. The example search strategy in Table 1 will be used for Pubmed. The search strategy for each of the other sites is adapted to the characteristics of the database. We will search the list of related references for more trials and existing systematic reviews (SRs) related to our topics by PubMed and Cochrane Library, and will also search a reference list to identify published journals related to the research topic, Books, conference articles, and grey literature.

2.4. Criteria for including studies

2.4.1. Types of studies. This article only reviewed the RCT of acupoint injection as the main treatment. The control group included oral medication, non-acupoint, no treatment, placebo, diet and so on. In addition, both Chinese and English publications are subject to language restrictions. RCTs that are not subject to release status will be included, excluding the remaining types of documentation.

2.4.2. Types of participants. Regardless of race, gender, age, and education, in our SR patients must comply with the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, World Allergy Organization (EAACI/GA2LEN/EDF/WAO) guidelines\textsuperscript{[1]} or the Chinese guidelines for the diagnosis and treatment of urticaria version.\textsuperscript{[59]}
Table 1
The search strategy used in PubMed.

| No | Search items |
|----|--------------|
| 1  | Urticaria (all field) |
| 2  | Chronic urticaria (all field) |
| 3  | Hives (all field) |
| 4  | Rubella (all field) |
| 5  | Wind cluster (all field) |
| 6  | Acupuncture (all field) |
| 7  | Acupuncture point injection (all field) |
| 8  | Hydro-acupuncture (all field) |
| 9  | Acupuncture block (all field) |
| 10 | Acupuncture-injection (all field) |
| 11 | Acupoint injection (all field) |
| 12 | Acupoint injection (all field) |
| 13 | Acupoint injection (all field) |
| 14 | Acupoint injection (all field) |
| 15 | Acupoint injection (all field) |
| 16 | Acupoint injection (all field) |
| 17 | Acupoint injection (all field) |
| 18 | Acupoint injection (all field) |
| 19 | Acupoint injection (all field) |
| 20 | Acupoint injection (all field) |
| 21 | Acupoint injection (all field) |
| 22 | Acupoint injection (all field) |
| 23 | Acupoint injection (all field) |
| 24 | Acupoint injection (all field) |
| 25 | Acupoint injection (all field) |
| 26 | Acupoint injection (all field) |
| 27 | Acupoint injection (all field) |

2.4.3. Types of interventions and comparisons. Qualified interventions in the trial group were based on sterile syringes. Interventions include acupoint injection of BCG-PSN alone or in combination with other active therapies for CU. If combined with other methods, only the control group with the same intervention measures as the experimental group was included. The trial group such as Acupoint injection BCG-PSN combined with other traditional Chinese therapies (eg, Chinese herb decoction, acupuncture, and other therapies), Acupoint injection BCG-PSN versus non-acupoint injection, will be excluded. The following processes will be compared:

1. Acupoint injection of BCG-PSN versus no treatment.
2. Acupoint injection of BCG-PSN versus other active therapies.
3. Acupoint injection of BCG-PSN plus active therapy versus the same active therapies.
4. Acupoint injection of BCG-PSN versus placebo or sham Acupoint injection.

2.4.4. Types of outcomes.

2.4.4.1. The primary outcomes. The primary outcome was disease activity control, measured by the urticaria activity score (UAS), urticaria control test (UCT), or other validated symptom scores.

2.4.4.2. The secondary outcomes.

1. Response rate.
2. Recurrence rate during the follow-up period.
3. Adverse events.

2.5. Data collection and analysis

2.5.1. Selection of studies. References from the search results will be added to the EndNote software (V.X8) document management software and duplicate content will be deleted. Two review authors (XX and LZ) will independently review and screen the titles, abstracts, and keywords of all retrieved studies to confirm eligible trials. The reviewer will receive a full report for further evaluation. Excluded explanations will be recorded in the excel data set. The disagreement between the reviewers (XX and LZ) is still unsolvable by discussion and is determined by a third party's arbitration (YC).

2.5.2. Data extraction and management. The 2 review authors (YL and QZ) will extract data independently from the selected report or study and fill out the data extraction form. Extract the following information: general information, participants, methods, interventions, results, results, adverse events, main conclusions, conflicts of interest, ethical approval, etc. When the reported data is insufficient, we will contact the author for more information. In this process, any inconsistencies will be resolved through discussion between the 2 authors or judged by the third author (LW).

2.6. Assessment of risk of bias in included studies

The 2 authors (WC and QZ) will assess the study quality by using the checklist developed by the Cochrane Collaboration’s risk assessment tool which evaluates the presence of potential selection bias (random sequence generation and allocation concealment), performance bias (blinding of investigators and participants), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting) and possible other sources of bias (funding bias). This review uses L, U, and H as the key to these assessments, where L (low) indicates a lower risk of bias, U (unclear) indicates that the risk of bias is uncertain, and H (high) indicates a higher risk of bias. If inconsistent results appear, the final decisions will be made by the third author (SZ).

2.7. Measures of treatment effect

For dichotomous data, risk ratio with 95% confidence interval (CIs) will be used to measure the treatment effect. For continuous data, mean difference (MD) and 95% CIs were used to measure treatment effectiveness.

2.8. Dealing with missing data

We will handle missing data in accordance with the guideline stipulated in the Cochrane Handbook for SRs of Intervention. In particular, the following methods will be used:

1. Contact the corresponding author to request missing data.
2. Perform analysis of available cases.
3. Discuss the potential impact of missing data.

2.9. Assessment of heterogeneity

Statistical heterogeneity will be assessed for significance with the Cochran Q test statistic[61] and quantified with the I² value.[62] If statistically significant, the cause will be discussed by narration and the use of subgroups and sensitivity analysis.
2.10. Assessment of reporting biases

We will evaluate publication bias using the Egger test and funnel plots.\textsuperscript{[63]}

2.11. Date synthesis

We will use Review Manager 5.3 for all statistical analyses. The data will be pooled for the meta-analysis when the included studies are sufficiently homogeneous with respect to subjects, interventions, and outcomes. All similar studies will be pooled for a random-effects model to obtain the pooled intervention effect. The pooled intervention effect will be expressed in terms of the MD and 95\% CI if the outcome was reported as a continuous variable. If different scales were used to assess the outcome, the standard MD will be used. If the outcome was measured as a dichotomous variable, we will convert the OR into the standard MD as long as the underlying continuous measure followed an approximately normal distribution.

2.12. Subgroup analysis

To resolve some potential problems, we will perform a subgroup analysis. First, we will compare the results of different drug injections at acupoints. Second, we will compare the results of acupoint injection alone with those combined with other active treatments.

2.13. Sensitivity analysis

To verify the robustness of the conclusions, sensitivity analyses will be performed to examine the impact of including low-quality studies in the meta-analysis and exclude studies with high or ambiguous bias risk.

2.14. Grading the quality of evidence

We will judge the quality of evidence of the results by grading the methods of the recommendations, assessments, developments, and assessments of the working group. Risk of bias, consistency, directness, accuracy, publication bias and additional points were the areas we assessed. The assessment results will be divided into 4 levels: high, moderate, low, or very low.

3. Discussion

CU is a disease with high incidence and seriously affects the quality of life and work of patients, but many patients are not
satisfied with the current treatment. Acupuncture injection of BCG-PSN is an important therapy of integrated Chinese and western medicine. Many studies at home and abroad have shown that it has a considerable effect on CU, and has the advantages of simple operation and low cost, but its clinical evidence is insufficient and adverse reactions have been reported. As a drug commonly used in China to treat CU, BCG-PSN has been shown to be effective in many studies, while some studies have not found the effectiveness of its combination. This SR will summarize the efficacy and safety of the current evidence and hope to provide convincing evidence for patients and clinicians during the decision-making process.

Author contributions

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