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Efficacy and safety of acupuncture for chemotherapy-induced leucopoenia: protocol for a systematic review

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ABSTRACT

Introduction: Many cancer patients experience leucopoenia during chemotherapy. Granulocyte-colony-stimulating factor (G-CSF) is used to treat chemotherapy-induced leucopoenia (CIL) but has various limitations. Clinical trials have indicated that acupuncture may prevent bone marrow suppression and increase leucocyte counts after chemotherapy. The objective of this review is to assess the efficacy and safety of acupuncture for treating CIL.

Methods and analysis: This systematic review will electronically search the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, Medline, EMBASE, the China National Knowledge Infrastructure Database (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (VIP Database) and the Wanfang database from their inception to 1 January 2016. Other sources will also be searched including potential grey literature, conference proceedings and the reference lists of identified publications and existing systematic reviews. Two reviewers will independently search the databases, perform data extraction and assess the quality of studies. Data will be synthesised by either the fixed-effects or the random-effects model according to a heterogeneity test. White blood cell counts will be assessed as the primary outcome. Adverse effects, incidence of leucopoenia, quality of life and physical condition will be evaluated as secondary outcomes. RevMan V.5.3 will be employed for data analysis. The results will be expressed as risk ratios for dichotomous data and mean differences for continuous data.

Ethics and dissemination: The protocol does not need ethics approval because individuals cannot be identified. The review will be reported in a peer-reviewed publication or at a relevant conference.

Trial registration number: CRD42015027594.

INTRODUCTION

According to recent data, cancer continues to be a serious worldwide health problem and is a leading cause of disease-related death.[1–3] Chemotherapy is one of the main cancer treatments but can be affected by dose-limiting toxicity, with leucopoenia being a common adverse effect.[4] Leucopoenia is defined as a decrease in the number of circulating white blood cells (WBCs) to counts of less than 4×10^9/L.[5] This can result in life-threatening infection,[6] dose reduction and chemotherapy delays,[7] affecting treatment success. Although medications, such as granulocyte-colony stimulating factor (G-CSF) or CSFs are used as prophylactic measures to reduce the depth and duration of chemotherapy-induced leucopoenia (CIL),[8] dose-intensity administration is required to sustain pharmacological efficacy.[9 10] The consequent increase in frequency or dose can, in turn, cause bone pain, myalgia, fever, rashes and other adverse reactions.[11] In addition, supplementing chemotherapy with G-CSF has been reported to result in acute myeloid leukaemia or myelodysplastic syndrome,[12] even stimulating angiogenesis and promoting tumour growth.[13] Nevertheless, CSFs are recommended in guidelines for use in patients who have a 20% or higher risk of febrile neutropenia or have ever experienced a neutropenic complication from a previous chemotherapy cycle. This means that not every patient with CIL, or even those with a lower risk of febrile neutropenia, can be treated with G-SCF/CSFs.[14] Considering the limited scope for application of these medications and their adverse effects, it is essential to introduce other interventions in order to benefit more patients.

Acupuncture, which is a therapy that stimulates specific points on the body surface, has been used for the prevention and treatment of diseases for thousands of years in China and other Eastern countries. Many recent clinical trials and animal studies have reported that acupuncture could alleviate CIL, while having fewer side effects and a relatively lower cost compared to G-CSF/CSF.[15] In traditional Chinese medicine, acupuncture is

believed to function by stimulating acupoints to regulate and balance Qi circulation.[16] In Western medicine, the mechanism involved has not been well established.[17] Studies in animals and humans have suggested that acupuncture might play a positive role in preventing leucopoenia by stimulating anticancer immunity, promoting the protective effects of bone marrow[18 19] or increasing the activity of serum colony-stimulating factor.[20 21]

An increasing number of studies on acupuncture for treating CIL have been published in recent years. Some studies reported acupuncture could decrease the occurrence of leucopoenia or stimulate the activity of G-CSF. An exploratory meta-analysis of acupuncture for CIL published in 2007 found that acupuncture was associated with an increase in leucocytes ($p<0.0001$).[22] However, the methodological quality of these reviews was not good enough to support strong recommendations. The acupoints and matching acupoints with optimal efficacy for the treatment of CIL still remain unidentified. This review aims to systematically synthesise the primary research exploring the efficacy and safety of acupuncture for treating CIL.

METHODS AND ANALYSIS

Inclusion criteria for study selection

Types of studies

Randomised controlled trials (RCTs) will be included, while animal studies, case reports, commentaries or quasi-RCTs will be excluded.

Types of patients

Studies on cancer patients with CIL will be included regardless of age (>18 years old), gender, race, educational status, tumour type and stage, while studies whose participants had a primary disease of the haematopoietic system or a psychiatric disorder will be excluded.

Types of interventions

Experimental interventions

Acupuncture is defined as stimulation of acupoints by needles, and includes body acupuncture, scalp acupuncture, manual acupuncture, auricular acupuncture, electroacupuncture, fire needling and plum blossom needling. Studies of acupuncture used in experimental groups will be included. Studies of other forms of stimulation including acupressure without needles, moxibustion (other than a warming needle method), transcutaneous electrical nerve stimulation, laser acupuncture or drug injection therapy will be excluded.

Comparator interventions

All studies in which patients in the control group were treated with acupuncture will be excluded except studies that carried out sham acupuncture in the control group. All studies in which patients received radiotherapy, molecular targeted therapy or Chinese herbal medicine will also be excluded.

We will investigate following treatment comparisons:

1. Acupuncture versus no treatment
2. Acupuncture versus sham acupuncture[23]
3. Acupuncture versus other treatment
4. Acupuncture with another treatment versus the same treatment without acupuncture.

Types of outcome measures

Primary outcomes

The primary outcome will be changes in WBC counts from baseline to the endpoint. We will contact the authors of original articles for additional information about the primary outcome if it is expressed as changes in the rate of decrease in WBCs at grades I–IV (according to the criteria of the WHO Toxicity Grading Scale for Determining the Severity of Adverse Events, 2003).

Secondary outcomes

The secondary outcomes will be:

1. Decrease in the incidence of leucopoenia (number needed to treat, NNT)
2. Incidence and type of adverse events due to acupuncture (eg, acupuncture-related infection, fainting during acupuncture treatment, sticking of needle)
3. Quality of life or physical condition, as measured by validated instruments (eg, the Karnofsky Performance Score (KPS), the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

Search methods for identification of studies

Electronic searches

We will electronically search the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, Medline (via PubMed), EMBASE (via embase.com), the China National Knowledge Infrastructure Database (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (VIP database) and the Wanfang database from their inception to 1 January 2016. The following search terms will be used: acupuncture, manual acupuncture, electroacupuncture, fire needling, auricular acupuncture, ear acupuncture, dermal needle, plum blossom needle, leucopoenia, leukopoenia, aleucocytosis, aleukocytosis, hypoleucocytosis, hypoleukocytosis, oligoleukocythemia, oligoleukocytosis, hypoleukia, G-CSF, Granulocyte colony-stimulating factor, GM-CSF and Granulocyte monocyte colony-stimulating factor. The search words with the same meaning as the English version will be used in Chinese databases. The search will be restricted to the English or Chinese language and human subjects. The search strategy for Medline (via PubMed) is shown in table 1. The search strategies used for EMBASE, CENTRAL, CNKI, CBM, VIP and the Wanfang database are supplied in online supplementary appendices 1–4.

Table 1 Search strategy used in PubMed

No.	Search items
1	Acupuncture therapy [mh]
2	Acupuncture [tiab]
3	Acupoints [tiab]
4	Body acupuncture [tiab]
5	Scalp acupuncture [tiab]
6	manual acupuncture [tiab]
7	Auricular acupuncture [tiab]
8	ear acupuncture [tiab]
9	Electroacupuncture [tiab]
10	Fire needling [tiab]
11	dermal needle [tiab]
12	plum blossom needle [tiab]
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	Leucopenia [mh]
15	Leukopenia [tiab]
16	Aleucocytosis [tiab]
17	Aleukocytosis [tiab]
18	Hypoleucocytosis [tiab]
19	Hypoleukocytosis [tiab]
20	oligoleukocythemia [tiab]
21	Oligoleukocytosis [tiab]
22	Hypoleukia [tiab]
23	G-CSF [tiab]
24	Granulocyte colony-stimulating factor [tiab]
25	GM-CSF [tiab]
26	Granulocyte monocyte colony-stimulating factor [tiab]
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	randomized controlled trial [pt]
29	controlled clinical trial [pt]
30	randomized [tiab]
31	placebo [tiab]
32	clinical trials as topic [mesh: noexp]
33	randomly [tiab]
34	trial [ti]
35	28 or 29 or 30 or 31 or 32 or 33 or 34
36	13 and 27 and 35

Searching other sources

The reference lists of potentially eligible studies and relevant systematic reviews will be manually retrieved and examined for additional trials. Relevant conference proceedings will also be searched to identify further studies. We will also search OpenGrey.eu for potential grey literature. In addition, we plan to search relevant trial protocols through the WHO International Clinical Trial Registry Platform (ICTRP) and ClinicalTrials.gov for ongoing and recently completed studies.

Data collection and analysis

All reviewers have received training to familiarise them with the purpose and process of the review. Studies obtained from electronic searches and other sources will be uploaded to a database created using Endnote X7. Two reviewers (XS and JG) will independently screen the titles, abstracts and keywords of all retrieved records. Studies meeting the predefined eligibility criteria will be included for full text screening, but their duplicates will be excluded. All excluded studies will be recorded in a 'Reasons for excluded studies' table. Any disagreement will be resolved by discussion between the two reviewers (XS and GJ) to achieve consensus; the arbiter (CY) will be consulted when necessary.

Data extraction and management

Two reviewers (XS and GJ) will independently extract data from selected studies and fill in the data extraction form which has already been developed. The authors of trials will be contacted for further details if necessary. We will extract the following information:

1. General information for the articles including the first author, year, country, sample size
2. Demographic characteristics including gender, age and other information including tumour type and tumour stage
3. Intervention parameters including type of acupuncture, acupoints used, chemotherapy drugs, other treatment, and frequency and duration of treatment
4. Outcome information including results, adverse events, costs and quality of life.

The data extraction sheet is supplied in online supplementary appendix 5.

Assessment of risk of bias in included studies

The risk of bias in all studies will be assessed by two reviewers (XS and GJ) using the Cochrane Collaboration's 'Risk of Bias' Tool, which includes the following seven domains: randomised sequence generation, allocation concealment, blinding of participants and personnel, binding of outcome assessment, incomplete outcome data, selective reporting and other issues. Each domain will be categorised into one of three levels of bias (low, unclear and high) and a 'Risk of bias' table will be filled in. Any discrepancies will be resolved by discussion between the two reviewers (XS and GJ) or by consulting a third reviewer (CY).

Measures of treatment effect

Mean difference (MD) with 95% CIs will be used to assess continuous outcomes, while dichotomous outcomes will be expressed as the relative risk (RR) with 95% CIs.

Unit of analysis issue

Only first-phase data will be assessed in randomised cross-over trials to prevent carry-over effects. In the case of studies with multiple intervention groups, we will carry out pairwise comparison if the groups meet the predefined inclusion criteria. Non-randomised controlled trials will not be included for analysis.

Dealing with missing data

We will attempt to contact the original investigators by email or by phone to obtain any missing or inadequate

data when lack of data prevents a study from being included. If we are unable to obtain missing data, analyses will be based on those patient populations in which outcomes were reported. Where studies report statistics based on intention-to-treat (ITT), we will perform case analyses when possible.

Assessment of heterogeneity

Heterogeneity will be assessed by visually inspecting the forest plot and investigated by χ^2 (significance level: $p<0.10$) and I^2 statistics. $I^2<50\%$ will be taken as evidence of no statistical heterogeneity, while $I^2\geq50\%$ will be considered to indicate substantial heterogeneity. The causes of heterogeneity among study results will be explored through subgroup analysis or sensitivity analysis.

Assessment of publication biases

We will generate funnel plots to detect publication bias or small-study effects using sufficient numbers of included studies (at least 10 studies).

Data synthesis

RevMan V.5.3 will be employed for data analysis when meta-analysis is possible. The MD with 95% CIs will be used to assess continuous outcomes, while the RR with 95% CIs will be used for dichotomous data. If $I^2<50\%$, the RR and MD will be calculated by a fixed-effects model. If $I^2\geq50\%$, a random-effects model, will be used to synthesise the data and subgroup analysis or sensitivity analysis will be conducted to explore the causes of heterogeneity including clinical or methodological reasons. We may conduct narrative synthesis if meta-analysis is not appropriate (eg, incidence of adverse events of acupuncture).

Subgroup analysis

We will perform subgroup analysis to explore possible causes of heterogeneity if there are an adequate number of studies (at least 10 trials). The effect of different types of acupuncture therapies and CSF (G-CSF/GM-CSF) will be included for analysis. We will also remove studies with low and/or medium quality in order to examine the robustness of the results.

Sensitivity analysis

Sensitivity analysis will be used to determine whether the conclusions are robust to the decisions made during the review process. We will conduct a one-study-removed analysis by excluding one study in turn and reanalysing the remaining studies in order to explore potential effects on the composite endpoint.

Grading the quality of evidence

We will use Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the quality of confidence for primary outcomes.[24] The quality of evidence will be classified into four levels: high, moderate, low or very low.

DISCUSSION

CIL is one of the most common side effects during chemotherapy. It can result in severe adverse reactions which may affect the efficacy of treatment. The use of G-CSF has resulted in a significant reduction in leucopoenia. However, per-cycle administration (daily use), adverse events, the cost and the need for expensive antineoplastic agents have limited its clinical application. Studies have reported that acupuncture could prevent the decline in WBCs and could be used as an adjunct to medications to increase the activity of G-CSF, while having fewer side effects and relatively lower cost. However, the quality of current evidence has not been determined. Therefore, we will conduct a systematic review in order to provide more convincing evidence for clinicians. This systematic review will consist of four sections: identification, study inclusion, data extraction and data synthesis.

Some potential limitations may affect conclusions drawn during the review. First, restricting the electronic search to the English and Chinese languages may limit the search for potential studies, such as articles in Japanese, Korean or German. Second, any ongoing or unpublished studies will not be able to be included. Third, the various types of acupuncture used, diverse chemotherapy drugs, mixed tumour types and different stages may increase the risk of heterogeneity. Finally, difficulty in undertaking blinding measures during acupuncture may bias the results.

The PRISMA-P checklist of the protocol is supplied in online supplementary appendix 6.

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Contributors XW is the guarantor of the article. JN and XS drafted the manuscript. LY and JN developed the search strategy. XS and JG will independently screen the potential studies, perform data extraction, assess the risk of bias, enter data into RevMan and finish data synthesis. CY will arbitrate any disagreements and ensure no errors occur during the review. GY, MY and GZ all contributed to the conception, design, revision and final approval of the article. All authors read and approved the final manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Protocol amendments If it is necessary to amend the protocol, we will provide a detailed explanation of the date, the change and the rationale.

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