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Review article

Effects of auricular acupressure therapy for preventing constipation in leukemia patients undergoing chemotherapy: Protocol for a systematic review

Xiao-rong Liu[a,*,1], Liu Feng[b,1], Rana Nicole[c], Ng-Shin Wong[c]

[a] Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China
[b] Department of Laboratory Medicine, Southwest Hospital, The Army Medical University (Third Military Medical University) Chongqing, China.
[c] School of Health and Biomedical Sciences, Royal Melbourne Institute of Technology University, Bundoora, Victoria, Australia

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ABSTRACT

Introduction: Auricular acupressure therapy is widely used in East Asia and Europe to prevent constipation in leukemia patients undergoing chemotherapy. The aim of this systematic review will be to evaluate the available evidence from randomized controlled trials (RCTs) of auricular acupressure therapy for preventing constipation in leukemia patients undergoing chemotherapy.

Methods: The following databases will be searched from their inception until May 2017: MEDLINE, CINAHL, EMBASE, AMED, the Cochrane Central Register of Controlled Trials and four Chinese databases [Chinese BioMedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wan-Fang Data and Chinese WeiPu Database]. Only the RCTs related to the effects of auricular acupressure therapy on preventing constipation in leukemia patients undergoing chemotherapy will be included in this systematic review. A quantitative synthesis of RCTs will be conducted using RevMan 5.3 software. Study selection, data extraction, and validation will be performed independently by two reviewers. Cochrane criteria for risk-of-bias will be used to assess the methodological quality of the trials.

Ethics and dissemination: This systematic review will not use data from individual patients and no privacy issues will be violated. The results will be disseminated through peer-reviewed publications.

Trial registration number: PROSPERO registration number: CRD42017067880.

1. Background

Constipation is a frequent health-related issue and a common side effect in leukemia patients treated with chemotherapy. According to a recent study, leukemia patients receiving chemotherapy may suffer with a high incidence of constipation (50%–80%), and the risk is increasing [1]. In leukemia patients treated with chemotherapy, constipation can cause loss of appetite, abdominal distension accompanied by the abrupt abdominal pain, hemorrhoids, and rectal tearing [2]. Moreover, untreated constipation may progress to fecal impaction, intestinal obstruction and even sepsis [3]. Furthermore, chemotherapy-induced constipation may impair patients' normal quality of life and result in the severe psychological symptoms such as anxiety and stress [4]. Hence, the prevention of constipation among leukemia patients undergoing chemotherapy is necessary in the clinical practice.

1.1. Description of the condition

To date, the recent research recommended that the administration of both oral and/or rectal laxatives may have beneficial effects to manage the chronic constipation [4]. However, leukemia patients receiving chemotherapy usually require additional interventions to alleviate the symptoms of constipation [5]. Moreover, these drugs are frequently associated with some undesired side effects, and increase the risk of serious adverse events (AEs) involving the electrolyte and mineral imbalances, severe dehydration and laxative dependence [6]. Therefore, patients receiving chemotherapy in East Asian often tend to seek complementary and alternative medicine (CAM) therapies for help in managing their constipation [7].

* Corresponding author.
E-mail address: liuxiaorongsu@163.com (X.-r. Liu).
[1] These authors contributed equally to this article.

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1.2. Description of the intervention

Auricular acupressure (AA) is a major integral part of CAM. It is described as a technique that involves Semen vaccariae (wang bu liu xing) seeds, Semen raphani (lai fu) seeds, Semen sinapis Albae (bai jie) seeds or magnetic pellets with an adhesive tape on certain acupuncture points of ears [8]. In 1990, AA was regarded as a form of micro-acupuncture that may have an effect on the holistic human system [9]. Thus, the therapeutic effects can be achieved by stimulating specific acupuncture points of the ear that are connected to certain organs or systems of the body. To date, the research on AA has two main theories. Based on meridian theory in China, the ear is associated with 12 meridians, and continuously stimulating the ear can improve vital energy (Qi) and remove the blood stasis [10]. Based on reflexology theory in Europe, AA has been applied systematically since Nogier discovered the auricular microsystem in 1957 [11]. Currently, AA, as a non-invasive traditional procedure, has been widely accepted by CAM practitioners and patients in East Asian [12]. According to a 2011 cross-sectional study, AA was considered as the most widely used CAM therapy in South Korean [13]. What is more, a vast majority of the Traditional Korean Medicine doctors have applied this technique for treating different kinds of diseases in TCM clinics, especially for end-stage oncological diseases [13]. In addition, a population-based survey conducted in Mainland China also revealed that almost one-fourth of the oncological patients employed AA for managing their chemotherapy- induced side effects [14]. Recently, according to the international guideline from the Oncology Nursing Society, AA has been recommended as a suitable and promising technique for the management of chemotherapy-induced side effects [15,16].

1.3. How the intervention might work

The mechanism of action of AA is still not clear, and various theories have been proposed. In modern research, the primary speculation about AA is somatotopic arrangement theory. In 1980, doctor Oleson recruited 40 patients with specific musculoskeletal pain condition in a double-blind research to examine whether somatotopic arrangement theory corresponded to parts of the body and they obtained a 75.2% accuracy rating [17]. In addition, there are various neurophysiological connections between auricular reflex points and the autonomic and central nervous system. Thus, groups of pluripotent cells contain information from the whole autonomic and central nervous system attempt to create regional organization centers representing different parts of the body [18]. In 1998, a U.S. scholar, Choy, discovered that application of ear clips to the tragus may induce obvious changes in gastrointestinal peristalsis. He reported that the frequency of peristalsis was changed by clips on the ear and returned to normal with the clips off [19]. Therefore, the ears are the closest organs to the brain, and the application of AA in the auricular reflex points associated with gastrointestinal function may have a beneficial effective on alleviating constipation symptoms [20]. From the TCM perspective, the constipation falls under the heading of *BianJie*, which is attributed to 'dysfunction of spleen in transportation' and 'stomach disharmony'. According to the theory of TCM, AA stimulates acupuncture points on ears, which could reinforce qi circulation and affect nourishment of the spleen, leading to an improved *Bian Jie* state [21]. Overall, the above basic modern scientific and TCM researches may partly account for the possible mechanism of AA, and provide a better understanding of the mechanism of AA.

1.4. Why it is important to do this review

Recently, a bibliometrics analysis of papers published from 1994 to 2012 in China showed that AA has been widely used in preventing various chemotherapy-induced side effects, including constipation [22]. Nowadays, numerous systematic reviews have investigated the effects of AA on insomnia [23], postoperative pain [24], and vitro fertilization [25]. Nevertheless, there has been no systematic review specifically focusing on the efficacy of AA for preventing constipation in leukemia patients undergoing chemotherapy.

Therefore, the aim of this study is to update and critically evaluate the evidence from randomized controlled trials (RCTs) that have tested the efficacy and safety of AA in preventing constipation in leukemia patients undergoing chemotherapy.

2. Methods

2.1. Study registration

We will follow the reporting guidelines in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist. [26]. In addition, the protocol of this systematic review has been registered in PROSPERO (Registration Number: CRD42017067880).

2.2. Ethics and dissemination

A formal ethical approval is not required because this research will not use data from individual patients and no privacy issues will be involved. The results will be disseminated through peer-reviewed publications.

2.3. Criteria for considering studies for this review

2.3.1. Types of studies

Only the RCTs related to the effects of AA for preventing constipation in leukemia patients receiving chemotherapy will be included in this systematic review. Trials published in the form of dissertations will also be selected as eligible studies. No language restrictions will be imposed.

2.3.2. Types of participants

Patients with leukemia and more than 18 years of age undergoing chemotherapy will be included in this research.

2.3.3. Types of interventions

2.3.3.1. Control interventions. A sham AA/placebo or routine care as controls will be included. The routine care will involve appropriate physical exercises, dietary modification (water intake > 3000 mL/d and fiber consumption) as well as psychological interventions [27]. If leukemia patients undergoing chemotherapy present constipation (diagnosis according to the definitive Rome III criteria), laxatives treatments will be administered [28]. Studies is be excluded if the control group treatments is not relevant to routine care or other CAM therapies (e.g. acupuncture, moxibustion, Chinese herbals, Chinese patent medicine) and used as an adjunct treatment in conjunction with the routine care.

2.3.3.2. Experimental interventions. Studies will be included if AA is used as an adjunct therapy in conjunction with routine care for preventing constipation among leukemia patients undergoing chemotherapy. Considering that non-invasive AA is more common in the clinical practice. Thus, we only include the non-invasive AA intervention in this research. In addition, we will exclude studies in which other CAM therapies (e.g. acupuncture, moxibustion, massage, Chinese herbals, Chinese patent medicine) will be utilized as an adjunct treatment in conjunction with the routine care.

2.3.4. Types of outcome measures

2.3.4.1. Primary outcomes.

(1) Patient Assessment of Constipation–Symptom (PAC-SYM): is an

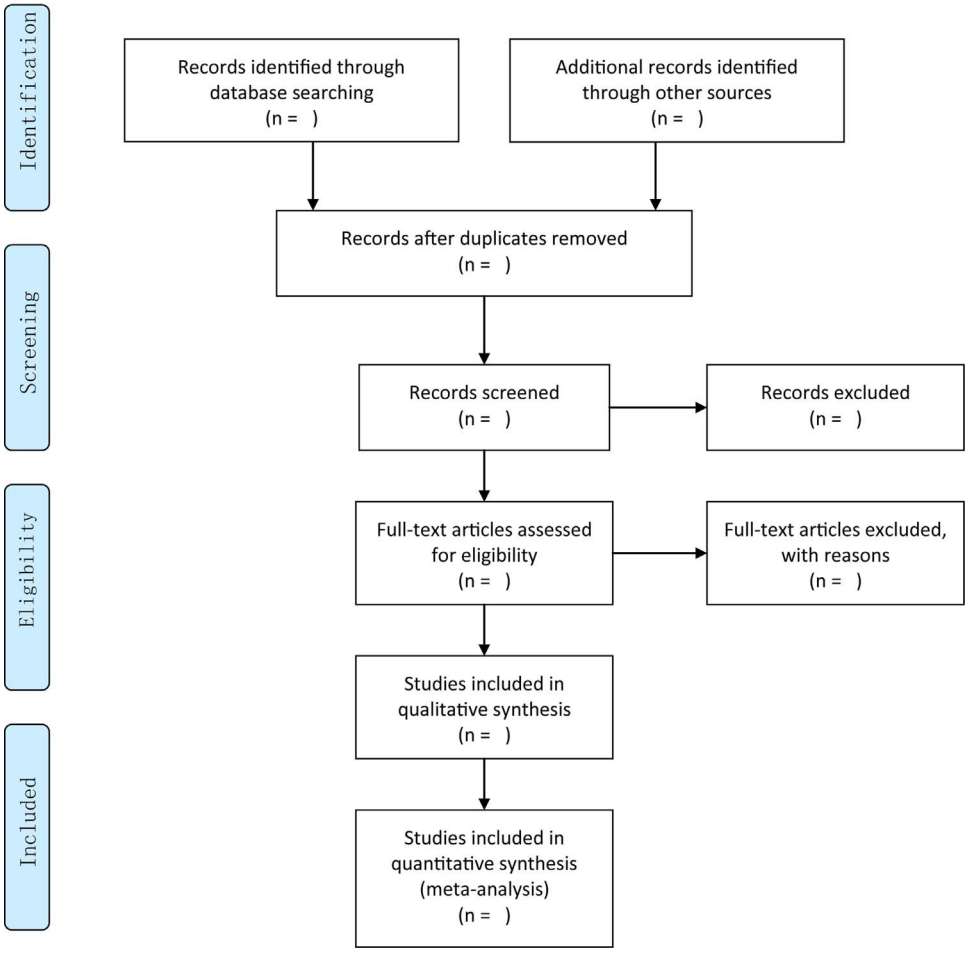

Fig. 1. The PRISMA flow diagram of the trial selection process.

internationally used validated questionnaire to determine patients' experience of constipation over time. This questionnaire consists of 12 items in three dimensions (abdominal symptoms 4 items; rectal symptoms 3 items; and stool symptoms 5 items). Each dimension has a score ranging from 0 to 4, resulting in a total score between 0 and 48. Higher scores in the respective scales indicate more severe symptoms [29].

(2) Constipation Assessment Scale (CAS): CAS score will be used to assess patients with constipation in the clinical settings [30]. This questionnaire includes 8 items. For each item, we have three possible response options: no constipation, some problem, and severe problem. The equivalent scores are 0, 1 and 2, respectively. The total CAS score ranges from 0 to 16 and higher scores can indicate higher degrees of constipation.

2.3.4.2. Secondary outcomes.

(1) Patient Assessment of Constipation–Quality Of Life (PAC-QOL): is a valid and reliable measurement containing 28 items in four dimensions (physical discomfort 4 items; worries and concerns 11 items; psychosocial discomfort 8 items; and satisfaction 5 items). Each item is rated using a five-point Likert scale from 0 (not at all) to 4 (extremely). Higher score indicates a more severe effect of constipation [31].
(2) Numbers of laxatives/week used by leukemia patients receiving chemotherapy.
(3) Adverse Events (AEs): The incidence and the severity of AEs from AA, the proportion of patients requiring discontinuation of AA.

2.4. Search methods for identification of studies

2.4.1. Electronic searches

The following databases will be searched from their inception until May 2017:

1. MEDLINE
2. CINAHL
3. EMBASE
4. AMED
5. Cochrane Central Register of Controlled Trials
6. Chinese BioMedical Database (CBM)
7. China National Knowledge Infrastructure (CNKI)
8. Wan-Fang Data
9. Chinese WeiPu Database
10. Korean Studies Information
11. DBPIA
12. The Korean Institute of Science and Technology Information
13. KERIS
14. KoreaMed
15. The Korean National Assembly Library
16. Japana Centra Revuo Medicina (http://www.jamas.gr.jp/)
17. CiNii

Search strategies which based on the guidance of the Cochrane handbook are presented in Appendix A, and these search terms will be slightly modified for other databases.

2.4.2. Searching other resources

2.4.2.1. The review will search.

1. In order to identify the grey literature/unpublished studies/incomplete trials, we will also identify relevant studies via a review of Chinese Clinical Trial Registry (http://www.chictr.org.cn/), Registry ClinicalTrials.gov (http://clinicaltrials.gov/), WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) and the Australian New Zealand Clinical Trials Registry (ANZCTR). Moreover, AA devices companies will also be requested to provide relevant published and unpublished data.
2. We will also search the reference lists of review articles or conference articles and identify RCTs for any possible titles matching the inclusion criteria.
3. Some important relevant Chinese-language articles published in *Journal of Clinical Acupuncture and Moxibustion*, *Acupuncture Research*, *Chinese Acupuncture and Moxibustion*, will be also handsearched from 1980 to May 2017.

2.5. Data collection and analysis

2.5.1. Selection of studies

Studies will be selected by two independent reviewers (Nicole and Wong). In most cases, disagreements will be resolved by discussion between the two reviewers. If disagreement remains after discussion, a third reviewer (Liu) will be consulted before taking the final decision on the disagreements. A flowchart depicting the trial selection process is shown in the PRISMA flow diagram (Fig. 1).

2.5.2. Data extraction

The complete text of each included article will be read by two independent reviewers (Nicole and Wong) who will extract relevant data based on a piloted data extraction form. The following data will be extracted from the original articles: (1) Author, year and country; (2) Diagnostic criteria and sample size; (3) Experimental interventions (different materials of AA, duration of treatment, auricular acupuncture points choosing); (4) Control Interventions (routine care interventions, types of laxatives, dose, methods of administration, and the duration of treatment); (5) Follow-up (6) Main Outcomes (7) AEs. All above information will be summarized in a data extraction table. Additionally, when reported data are insufficient, we will try our best to retrieve the missing information from the corresponding authors. Assessment of risk of bias in included studies.

The Cochrane risk of bias tool will be used to evaluate the methodological quality of each included trial by two independent reviewers (Nicole and Wong) [32], and each RCT will be assessed for the following characteristics: (i) selection bias; (ii) performance bias; (iii) detection bias; (iv) attrition bias; (v) reporting bias. The terms 'Low', 'Unclear', and 'High' referrers to low, uncertain, and high risks of bias, respectively. Disagreements will be resolved by discussion between the two reviewers. If consensus will not be reached, the third reviewer (Liu) will be consulted for a final decision.

2.5.3. Quantitative data synthesis and subgroup analysis

In our review, *meta*-analysis will be performed using software RevMan 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) [32]. For dichotomous data, we will present results as risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, mean difference (MD) will be included in the *meta*-analysis. If outcome variables are measured on different scales, standard mean differences (SMD) analysis with 95% CIs will be included in the *meta*-analysis. In each *meta*-analysis, the chi-square and I^2 tests will be used to evaluate statistical heterogeneity [33]. Given $I^2 < 50\%$ and $p > 0.1$, the studies will be considered to be homogeneous, and a fixed-effects model will be applied. On the other hand, if I^2 will be $\geq 50\%$ and $p < 0.1$, the trials will be considered to be heterogeneous, and a random effects model based on Mantel-Haenszel (MH) or inverse variance (IV) statistical approach will be selected [33]. The homogeneity is an important issue that we should resolve in this research. Thus, subgroup analysis will be conducted to interpret the heterogeneity between the studies. Subgroup analysis will be performed according to different factors as follows: 1.Patients' demographics (different types of leukemia and different types of chemotherapy regimens) 2. Different control interventions (A sham AA therapy or Routine care) 3.Different auricular acupuncture points (one point, two points or multiple points). 4. Different durations of follow-up (short-term, medium term or long term) 5. Different treatment frequency (less than three times per week or more than three times per week)

2.5.4. Unit of analysis issues

In case unit of analysis issues, if there are multiple treatment time observations, time frames will be defined as short-term (more than two weeks to twelve weeks), medium-term (more than twelve weeks to six months) and long-term (more than six months) follow-up, respectively. Additionally, if more than one AA arms are reported, we will conduct multiple *meta*-analysis using one treatment arm, respectively. If multiple control groups are used, each group will constitute a separate unit of analysis.

2.5.5. Dealing with missing data

If missing data are detected, we will try our best to request the missing or incomplete information from the corresponding authors. We will use an intention-to-treat (ITT) principle based on the last observation carried forward approach while analysing the outcomes. For dichotomous outcomes that measure benefits (e.g. Numbers of laxatives/week used by leukemia patients receiving chemotherapy), we will calculate the worst case analysis using the number of randomized subjects as the denominator. For continuous outcomes (e.g. PAC-SYM), we will calculate the last observation on each participant carried forward until the study endpoint.

2.5.6. Assessment of heterogeneity

Heterogeneity will be analyzed using a chi-square and I^2 tests. In addition, an alpha of 0.05 will be used for statistical significance [33]. I^2 values of 25%, 50% and 75% will be corresponded to low, medium and high levels of heterogeneity [33].

2.5.7. Sensitivity analysis

If the test for heterogeneity *p* value is less than 0.1 after performing the subgroup analysis, the sensitivity analysis will be conducted to evaluate the robustness of our results. The *meta*-analysis will be repeated after omitting the low-quality studies. Moreover, we will also assess whether the statistical model (random-effects vs fixed-effects model) will affect the current results.

2.5.8. Assessment of reporting biases

If a sufficient number of studies are available (at least 10 studies), we will attempt to assess publication bias using a funnel plot [34].

2.5.9. Grading the quality of evidence

We will apply the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method to evaluate the level of confidence in regards to outcomes [35]. Two independent reviewers (Nicole and Wong) will conduct the assessment. In most cases, disagreements will be resolved by discussion between the two reviewers. If disagreement will be remained after discussion, a third reviewer (Liu) will be consulted before taking the final decision on the disagreements.

2.6. Dissemination

To the best of our knowledge, this is the first systematic review protocol to provide the evidence regarding the use of AA as an adjunctive therapy for preventing constipation in leukemia patients

receiving chemotherapy. Previously, one systematic review of auriculotherapy for functional constipation in adults was published [36]. However, it is worth noting that the total numbers of RCTs and sample sizes were limited in that research. In addition, subjects in our research will be suffered from the chemotherapy-induced constipation. Furthermore, when compared to the previous systematic review, this research will provide readers the opportunity to obtain the original articles published in Chinese languages that they may otherwise be unable to read. Therefore, we believe the results of this study will provide more comprehensive and current evidence on the effectiveness and safety of AA therapy for the prevention constipation in leukemia patients undergoing chemotherapy. Moreover, we really hope that this research will help CAM practitioners and health policy makers to make decision regarding the appropriate role of AA as an adjunctive therapy when the leukemia patient undergoes chemotherapy.

Conflict of interest

No conflict of interest declared. Xiao-rong Liu and Liu Feng contributed equally to this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eujim.2017.09.002.

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