



Review article

Clinical effectiveness of acupuncture in the treatment of chemotherapy-induced leukopenia: A systematic review

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ABSTRACT

Introduction: Clinical studies have suggested that acupuncture may be useful in the treatment of chemotherapy-induced leukopenia, a commonly encountered adverse event experienced by cancer patients. The aim of this meta-analysis was to determine the clinical effectiveness of acupuncture for this indication.

Methods: A search for randomized controlled trials was carried out using the following databases; China National Knowledge Infrastructure (CNKI), Excerpta Medica dataBASE (EMBASE), Public/Publisher MEDLINE (PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL). The included trials were assorted into several subgroups according to the acupuncture type, and the rate of leukopenia was meta-analyzed in each subgroup. The methodological quality of these studies was assessed using the criteria for systematic reviews recommended by the Cochrane Collaboration.

Results: Four types of acupuncture were used in the included studies; conventional manual acupuncture (CA: 3 trials, n = 178), pharmacopuncture (PA: 3 trials, n = 187), warm needle acupuncture (WA: 1 trial, n = 57), and fire needle acupuncture (FA: 1 trial, n = 60). CA (RR, 0.62, 95% CI, 0.43–0.91; $P=0.01$) and FA (RR, 0.20, 95% CI, 0.05–0.84; $P=0.03$) reduced the leukopenia rate with statistical significance. The methodological quality was found to be insufficient, since all the included studies were at unclear or high risk of bias for at least two of six domains.

Conclusions: The results suggest that CA and FA might be beneficial for chemotherapy-induced leukopenia. However, more well-planned studies are still needed due to the small number of studies available for analysis and the considerable methodological flaws in the analyzed trials.

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1. Introduction

Chemotherapy is a main constituent of cancer treatment and most cancer patients receive chemotherapy at some time during their treatment [1–3]. However, chemotherapy may cause various adverse events, such as fatigue, appetite loss, nausea, diarrhea, alopecia, cognitive problems, and myelosuppression [1]. Leukopenia, which generally refers to a decrease in white blood cell (WBC) count fewer than 4000/mm³, is one of the most common side effects encountered with the use of myelotoxic anticancer agents [4]. Almost all patients who are undergoing chemotherapy are at risk for the occurrence of leukopenia, though the incidence varies according to regimen, dose, cancer type, etc [5]. For example, the bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-prednisone (BEACOPP) regimen, when it was administered in increased dose for the treatment of advanced-stage Hodgkin's disease, caused leukopenia grade 3 or 4 in 98% of subjects [6,7]. Chemotherapy-induced leukopenia is associated with life-threatening infections through impairment of the host's immune system [8]. Thus, it often prolongs duration of hospitalization and increases in-hospital mortality [9]. Moreover, leukopenia in cancer patients delays chemotherapy treatment and reduces drug dose intensity, which may compromise clinical outcomes in potentially curable cancer [10,11].

Granulocyte and granulocyte-macrophage colony-stimulating factors are currently available to restore the reduced leukocyte levels that result from chemotherapy [12,13]. Although these hematopoietic colony-stimulating factors are efficient, these agents are also associated with several adverse events, such as musculoskeletal pain, fever, allergic reactions (including anaphylaxis), alveolar hemorrhage, cutaneous vasculitis, respiratory distress syndrome, and splenic rupture [14,15]. In addition, the effects of this treatment hold out only during a short time as well as the costs are very high [16].

In a few animal studies, acupuncture was found to have an effect on white blood cell count and their activity [17,18]. Furthermore, some recent clinical trials showed that acupuncture could effectively alleviate leukopenia during chemotherapy with fewer adverse effects [19]. In a recent systematic review, moxibustion, which is similar with acupuncture in that it stimulates the same meridian system, was also presented as a potentially effective therapy on this indication [20]. A systematic review which suggested a therapeutic potential of acupuncture in the treatment of this condition was also published several years ago [21]. However, a definitive conclusion could not be drawn from this review due to the excessive clinical diversity and inferior quality of the published studies at that time. Therefore, in order to establish a more precise and updated conclusion, we have conducted a new systematic review on this topic that includes clinical trials that have been published in recent years.

2. Methods

2.1. Literature search

We searched for relevant literature in China National Knowledge Infrastructure (CNKI), Excerpta Medica dataBASE (EMBASE), Public/Publisher MEDLINE (PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL), using keywords related

to “acupuncture” and “chemotherapy-induced leukopenia”. The search formula was as follows: (chemotherapy OR cancer) AND (leukopenia OR neutropenia OR myelosuppression OR bone marrow suppression OR adverse event OR side effect) AND (acupuncture OR electroacupuncture OR acupoint OR pharmacopuncture). As for the search condition; the most comprehensive way was selected among available options in each database: ‘full text’ in CNKI; ‘search as broadly as possible’ in EMBASE; ‘all fields’ in PubMed; and ‘search all text’ in CENTRAL. For example; Search strategy used for CNKI was as follows: (FT=‘chemotherapy’ or FT=‘cancer’) and (FT=‘leukopenia’ or FT=‘neutropenia’ or FT=‘myelosuppression’ or FT=‘bone marrow suppression’ or FT=‘adverse event’ or FT=‘side effect’) and (FT=‘acupuncture’ or FT=‘electroacupuncture’ or FT=‘acupoint’ or FT=‘pharmacopuncture’). The publication date of articles was limited from their inception through to December 2014. The language of articles was not restricted.

2.2. Selection criteria

Studies were included that satisfied all of the following criteria: (1) Study design: randomized controlled trials that compared acupuncture with at least one control group receiving sham or no intervention. Studies that reported “randomly assigned to groups” were included, even if there was no description of an adequate randomization process. (2) Participants: adults who were diagnosed with cancer at any stage and with leukopenia related to chemotherapy, or scheduled to take chemotherapy. (3) Intervention: stimulation of acupuncture points through penetration of the skin with thin solid, metallic needles. (4) Outcome measure: rate of patients with leukopenia (WBC count < 4000/mm³) or other outcomes that can be converted to leukopenia rate.

The exclusion criteria were: (1) Non-randomized controlled clinical trials, case reports, animal studies, qualitative studies, review articles or reports that were available only in abstract form. (2) Studies with non-skin-penetrating stimulation of acupoints, including stand-alone acupressure, moxibustion, laser, and infrared. (3) Studies that co-administered other interventions, which could potentially influence WBC level, to only acupuncture group and not control group.

Two of the authors independently assessed the eligibility of the studies retrieved from the databases based on the selection criteria. Disagreements between authors were resolved through discussion.

2.3. Data extraction and assessment of methodological quality

The following data were extracted from each included study: Number of subjects, cancer types, chemotherapy agents, interventions for experimental and control groups, acupuncture type, acupuncture points targeted in the acupuncture treatment, number of total acupuncture treatments, study duration, method of outcome measure, and adverse events associated with acupuncture.

The methodological quality of all included studies was assessed using the risk of bias criteria from the Cochrane Handbook for Systematic Review of Interventions: the descriptions of random sequence generation, allocation concealment, blinding of

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