Acupuncture for chemotherapy-induced leukopenia: exploratory meta-analysis of randomized controlled trials

CRD summary
This review reported that acupuncture was associated with an increase in leukocytes in patients with chemotherapy-induced leukopenia. However, the authors concluded that, due to the poor quality of the trials and the likelihood of publication bias, the results should be treated as a hypothesis-generating exercise only. Despite weaknesses in the review process, the authors' cautious conclusions appear appropriate.

Authors' objectives
To evaluate the effectiveness and safety of acupuncture for chemotherapy-induced leukopenia and/or neutropenia in cancer patients.

Searching
The following databases were searched to June 2004: China Biological Medicine, Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), MEDLINE and EMBASE. In addition, the Cochrane Database of Systematic Reviews (Issue 4, 2004), the Cochrane Central Register of Controlled Trials, the internal database of non-MEDLINE journals housed in the New England School of Acupuncture Kelley Library and reference lists of retrieved articles were also searched. Publications in English and Chinese were eligible for inclusion.

Study selection
Randomised or quasi-randomised controlled trials evaluating acupuncture for cancer patients in conjunction with chemotherapy, or chemoradiotherapy or acupuncture immediately after chemotherapy, were eligible for inclusion. Eligible controls were chemotherapy alone or in conjunction with vitamins or non-herbal supplements. The outcomes of interest were white blood cell counts, absolute neutrophil counts and the number of responders. Trials of manual acupuncture, ear acupuncture, and electroacupuncture with metal needle insertion or needling insertions combined with other point stimulation methods, were eligible for inclusion. Trials of stand-alone non-skin penetration stimulation on acupuncture points were excluded. Trials of acupuncture point injection with corticosteroids or other biological agents, and Chinese herbal medicine were also excluded.

In the included trials, acupuncture methods varied between trials including manual acupuncture, electroacupuncture, warming needle and acupuncture point injection with saline. Frequency of treatment was once a day. The total number of treatments varied from three to 52 (median 16). Where reported, the median age of participants in the included studies was 47.9 years. Some participants in the included trials had already developed leukopenia. Cancer type varied between the trials including breast, lung, oesophageal, lymphoma, stomach, nasopharyngeal or was unclassified. Chemotherapy agents varied between included trials, as did white blood cell counts at baseline.

Two reviewers independently selected studies for inclusion. Disagreements were resolved through recourse to a third reviewer.

Assessment of study quality
Validity was assessed independently by two reviewers using the Jadad score (maximum possible score was 5 points). Two reviewers independently evaluated each included trial.

Data extraction
The mean difference between intervention and control for white blood cell counts, alongside 95% confidence intervals, were determined. An average increase of 1,000 white blood cells/L or greater was considered clinically meaningful and reflected one grade improvement for neutropenia.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
Data from individual trials were combined in a meta-analysis using a random-effects model to calculate the weighted mean difference and 95% confidence intervals for white blood cell counts. Heterogeneity was assumed a priori because of the different designs and environments in which the trials were conducted.

Sensitivity analyses were conducted for each two-arm trial and three-arm trial. Meta-regression and sensitivity analyses were conducted to check the treatment effects on predefined participant characteristics and to explore sources of heterogeneity.

The I² test was used to evaluate heterogeneity. Publication bias was assessed using visual examination of Begg's funnel plot and Egger's test.

Results of the review
Eleven (n=682) trials were included in the review. All eleven trials scored only 1 point on the Jadad validity scale, which was awarded because of reported randomisation. None of the trials used blinding or sham acupuncture as controls. No trials reported participant withdrawals or drop-outs. Follow-up was reported as short in many trials and participants did not complete full chemotherapy treatments. None of the trials reported power calculations.

The effective rates of leukopenia recovery with acupuncture varied between 57% and 90%.

The combined results (seven trials) reported a weighted mean difference of 1.221 (95% confidence interval (CI): 0.636 to 1.807; p<0.0001), indicating statistically significantly greater white blood cell s/μL (1,221 white blood cells/s/μL) in the acupuncture groups compared to control groups. Heterogeneity was high (I²=81%).

Sensitivity analyses for the multiple arm trials reported similar results. Sensitivity analysis also reported that electroacupuncture was significantly associated with leukocyte increase (weighted mean difference 1.863, 95% CI: 1.095 to 2.629; p=0.041) compared to control. Preload acupuncture and leukopenia present at baseline were not statistically significant predictors.

No adverse events were reported in any of the trials.

The level of publication bias was not statistically significant (data not reported).

Authors' conclusions
The results showed that acupuncture use was associated with an increase in leukocytes. However, due to the poor quality of the trials and the likelihood of publication bias, the results of this review should be treated as a hypothesis-generating exercise only.

CRD commentary
The inclusion criteria were clear in terms of intervention, participants, outcomes and study design. Several relevant sources were searched, with some attempts made to minimise language bias. No attempts were made to reduce publication bias but authors stated that formal assessment of publication bias suggested that this was not present in the review (although data were not presented); the search strategy was not reported in full, so can neither be evaluated nor replicated. Methods were used to minimise reviewer errors and bias in trial selection and the assessment of validity, but it was not clear whether similar steps were taken in data extraction. Validity was assessed using specified criteria and results of the assessment were reported.

There were considerable differences between trials in terms of participant diagnoses of cancer, as well as interventions and trial designs. There was also evidence of high statistical heterogeneity. In addition, only seven of the eleven included trials provided enough data to be included in the meta-analysis. Therefore, it may not have been appropriate to combine these trials in a meta-analysis. All the trials were conducted in China in hospitals, so the results may not be generalisable to other settings. The authors appropriately highlighted weaknesses in the included trials, including small sample sizes and poor quality. Despite weaknesses in the review process, the authors' cautious conclusions appear
appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a discipline-specific quality measure scale for acupuncture trials is needed and, given the subjective nature of acupuncture meta-analysis based on local trials, it should focus on exploring technical parameters, rather than aim for conclusive recommendations.

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