Effectiveness of different acupuncture therapies for chronic cancer pain
A protocol for systematic review and Bayesian network meta-analysis

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Abstract

Background: Pain is a common and distressing symptom experienced by cancer patients. Previous research found acupuncture was associated with significant reductions in pain intensity and opioid use. Acupuncture therapies are various, and the difference in efficacy and safety has never been assessed. This paper aims to assess and rank the effectiveness of the different acupuncture methods and provide an acupuncture treatment guideline for relieving chronic pain in cancer survivors.

Methods: Four English databases (PubMed, Embase, Cochrane library, and Web of Science) and 4 Chinese databases (China National Knowledge Infrastructure, Wanfang Data, and Chinese Biomedical Literature Database) will be searched for randomized controlled trials (RCTs) published from the database inception to November 30, 2021. The primary outcomes will be patient-reported pain intensity measured by the Brief Pain Inventory, Visual Analog Scale, Verbal Rating Scale, Numerical Rating Scale, and other valid outcome measures. The Grading of Recommendations Assessment, and Development and Evaluation System will evaluate the quality of evidence. Bayesian network meta-analysis will be performed in WinBUGS V.1.4.3 to determine the comparative effectiveness of the acupuncture therapies.

Results: This study will quantify the effectiveness of each acupuncture intervention for chronic cancer pain with pain scores and the use of analgesics. The adverse events of acupuncture treatment for cancer pain will also be reported.

Conclusion: The conclusion of our study will help physicians and patients choose suitable acupuncture methods to manage cancer pain.

Abbreviations: AA = auricular acupuncture, CI = confidence interval, Development and Evaluation, EA = electro-acupuncture, GRADE = Grading of Recommendations Assessment, MA = manual acupuncture, NCCN Guidelines = NCCN Clinical Practice Guidelines in Oncology, NRS = Numerical Rating Scale, PRISMA-P = the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, RCTs = randomized controlled trials, RevMan = Review Manager Software, RR = relative ratio, SUCRA = surface under the cumulative ranking curve, VAS = Visual Analogue Scale, VRS = Verbal Rating Scale.

Keywords: a systematic review, acupuncture, chronic cancer pain, network meta-analysis

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1. Introduction

1.1. Description of the condition

The number of cancer survivors was up to 15.5 million in 2016 in the United States and is expected to reach 26.1 million by 2040 with the aging population and advances in early diagnosis and treatment methods.[11] Pain, one of the most common and troublesome symptoms affecting patients with cancer, is experienced by 39% of cancer survivors, but inadequately controlled in nearly half of them.[12,13] Poor pain control is associated with impaired quality of life, lower adherence to treatment, and higher health care costs.[1,4]

Opioid analgesics are regarded as a gold standard in cancer-related pain, but clinicians must carefully assess whether their benefits counterbalance potential complications.[5] Opioid addiction among cancer survivors has been estimated to be as high as 7.7%.[6] Hundreds of thousands of individuals in the United States have died of opioid-related causes, billions have become addicted, and billions of dollars of economic value have been spent.[7] The ongoing opioid crisis in the United States has triggered new skepticism about opioid use and difficulties in cancer pain management.[8,9] Besides, nonpharmacologic methods are recommended for the treatment of adult cancer pain according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).[10]

1.2. Description of the intervention

Acupuncture, as one of the non-pharmacologic methods, has been successfully applied in the cure or relief of 64 different symptoms including pain,[11,12] and is available in over 78 countries, according to the World Health Organization (WHO, 2003).[13] Clinical evidence has demonstrated clinically significant relief of cancer pain and reduced use of analgesics by adopting acupuncture.[14,15] More than 20 systematic reviews have investigated the association of acupuncture with cancer pain; however, substantial heterogeneity lowered the level of certainty of the evidence.[15] The diversity of acupuncture therapies is likely a factor contributing to substantial heterogeneity.

Acupuncture therapies for cancer pain were shown as follows: Monotherapy, including manual acupuncture (MA), electro-acupuncture (EA), auricular acupuncture (AA); Combination therapy such as acupuncture with analgesics, manual acupuncture with auricular acupuncture, acupuncture with moxibustion.[15–18] Different acupuncture interventions will be included in the systematic review and network meta-analysis.

1.3. Objective

This study aims to assess and rank the effectiveness of different acupuncture therapies and provide a prioritized acupuncture-based treatment regimen for relieving chronic pain in cancer survivors by Bayesian network meta-analysis. Randomized clinical trials that compared acupuncture with sham control, analgesic therapy, or usual care for managing cancer pain will be included.

2. Methods

This protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement,[19] and has been registered in PROSPERO (CRD42020207158).

2.1. Eligibility criteria

2.1.1. Types of studies. All randomized controlled trials (RCTs) comparing acupuncture therapies with analgesics interventions, placebo, or no intervention for patients with cancer-related pain will be included without language or region restrictions. Studies with unavailable data will be excluded.

2.1.2. Types of participants. Patients (older than 18 years) who were diagnosed with cancer reported pain.[20] Pain resulting from the development of cancer self and/or cancer treatments will be included, but breakthrough or acute pain are excluded.

2.1.3. Types of intervention. Eligible interventions will be manual acupuncture, electro-acupuncture, auricular acupuncture, moxibustion, or a combination of these, regardless of acupoint selection, acupuncture manipulations, or treatment course. The control group can be sham acupuncture, analgesics, or usual care managing cancer pain. Trials comparing 2 acupoint selections (e.g., scalp acupuncture vs body acupuncture) or acupuncture manipulations (e.g., electroacupuncture vs manual acupuncture) will be excluded.

2.1.4. Types of outcome measure

2.1.4.1. Primary outcomes. Patient-reported pain intensity or pain relief measured by Visual Analog Scale (VAS), Verbal Rating Scale (VRS), the Brief Pain Inventory, Numerical Rating Scale (NRS), and other validated instruments. Results measured by different scales will be converted to the corresponding grade for data integration (0 points indicating no pain, and 10 points indicating most severe pain). Besides, pain lasting time after the intervention will be reported and included in the meta-analysis.

2.1.4.2. Secondary outcomes. Secondary outcomes will include Pain improvement percentage measured by valid scales such as VAS was calculated as (the pain score before treatment - the pain score after treatment)/ the pain score before treatment; Quality of life indicated by scales European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Consumption of analgesics or changes in concurrent treatments; and Adverse events of interventions.

2.2. Search strategy

Four English databases (PubMed, Embase, Cochrane library, and web of science) and 4 Chinese databases (China National Knowledge Infrastructure, Wanfang Data for Chinese Technical Periodicals, and Chinese Biomedical Literature Database) will be searched for RCTs published from the database inception to November 30, 2021. Date search comprised 3 components: clinical condition (i.e., cancer, tumor, neoplasm, carcinoma, pain, analgesia), intervention (i.e., acupuncture, manual acupuncture, electroacupuncture, auricular acupuncture), study type (RCT). The search strategy of the PubMed database is summarized in Table 1. In case of missing other eligible studies, reference lists of relevant publications, including trials, reviews, and meta-analysis, will be reviewed for a manual search.

2.3. Study selection and data extraction

All study selection will be independently performed by 2 reviewers (SL and HX) using a predetermined protocol according to the PRISMA flow diagram (Fig. 1).[19] Divergences between 2 reviewers will be solved by negotiating with a third reviewer.
Data extraction will be based on a standardized data form, including Trial characteristics (author, publication year, study design, location); Patient characteristics (sample size, age, gender ratio, cancer type, cancer treatment method, treatment status when receiving acupuncture); Details of intervention and control (form, acupoints, frequency and treatment duration); and Data of outcomes referred above.

### 2.4. Quality assessment

The quality of RCTs will be assessed with the Cochrane Collaboration risk of bias tool including 6 domains.[21] Six specific domains (sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective outcome reporting, and other potential threats), for each study, will be assigned a risk of bias (low, high,
2.5. Statistical analysis

2.5.1. Pairwise meta-analysis. The characteristics about participants, intervention, comparisons of the included RCTs will be summarized in the table. Continuous data will be performed by calculating the effect size and 95% confidence interval (95% CI) with a random-effects model, and dichotomous data will be computed with risk ratios. Heterogeneity among trials will be identified by the $\chi^2$ test and reported as $I^2$. STATA version 15.1 software (Stata Corporation, College Station, TX) will be used for statistical analysis. Two-sided $P < .05$ is regarded as statistical significance.

2.5.2. Network meta-analysis. The network meta-analysis will be conducted with a Bayesian hierarchical random-effects model using WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK) to combine and compare direct and indirect evidence of interventions for cancer pain. Inconsistency will be analyzed by both design-by-treatment and loop-specific approaches using a node-splitting test. The effect size for the continuous data will be calculated as a mean difference with 95% CIs, while dichotomous outcomes will be presented as risk ratios with 95% CIs. The surface under the cumulative ranking curve (SUCRA) will assess superiority probabilities of efficacy and safety outcomes for each intervention, and presented as percentages. Higher SUCRA values indicate better effects or safer intervention for cancer pain.

2.5.3. Subgroup analysis. In case of possible substantial heterogeneity, we will explore the possible sources using network meta-regression and subgroup analysis. Subgroup analysis will be stratified according to likely factors, including patients’ characteristics (i.e., age, gender), interventions, control group.

2.5.4. Sensitivity analysis. Sensitivity analysis will be performed to get a definitive conclusion of the review. Trials with missing data, small sample size, or rated as high risk of bias for methodological quality will be re-considered.

2.5.5. Assessment of publication bias. Publication bias of the included studies will be assessed by funnel plots and Egger’s test for asymmetry of primary outcomes.

3. Discussion

This study is expected to provide a ranking of acupuncture interventions for chronic cancer pain, regarding efficacy and safety by network meta-analysis. The results will help clinicians and patients choose preferred acupuncture therapy in the treatment of cancer pain. And we hope to provide evidence for policymakers to include effective and safe acupuncture therapies in the management of cancer. 

Author contributions

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References

[1] Jiang C, Wang H, Wang Q, et al. Prevalence of chronic pain and high-impact chronic pain in cancer survivors in the United States. JAMA Oncol 2019;5:1224–6.
[2] Henson LA, Maddocks M, Evans C, et al. Palliative care and the management of common distressing symptoms in advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. J Clin Oncol 2020;38:905–14.
[3] van den Beucken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51:1070–90.e9.
[4] Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin 2018;68:182–96.
[5] Arthur J, Bruera E. Balancing opioid analgesia with the risk of nonmedical opioid use in patients with cancer. Nat Rev Clin Oncol 2019;16:213–26.
[6] Chua IS, Leiter RE, Brizi KT, et al. US National Trends in opioid-related hospitalizations among patients with cancer. JAMA Oncol 2019;5:734–5.
[7] Sharfstein JM, Olsen Y. Lessons learned from the opioid epidemic. JAMA 2019;322:809–10.
[8] Smith EML. Pharmacologic treatments for chronic cancer-related pain: does anything work? J Clin Oncol 2019;37:1686–9.
[9] Vitzthum LK, Riviere P, Murphy JD. Managing cancer pain during the opioid epidemic-balancing caution and compassion. JAMA Oncol 2020;6:271
[10] Swarm RA, Paice JA, Angelhoucs-LDL, et al. Adult cancer pain, version 3.0, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:977–1007.
[11] Vickers Andrew J, Linde K. Acupuncture for chronic pain. JAMA 2014;311:955–6.
[12] Cummings M, Hrbojartson A, Ernst E. Should doctors recommend acupuncture for pain? BMJ 2018;360:k970.
[13] Lin J, Chen YH. The role of acupuncture in cancer supportive care. Am J Chin Med 2012;40:219–29.
[14] Miller KR, Patel JN, Symansow JT, et al. Acupuncture for cancer pain and symptom management in a palliative medicine clinic. Am J Hosp Palliat Care 2019;36:326–32.
[15] He Y, Guo X, May BH, et al. Clinical evidence for association of acupuncture and acupressure with improved cancer pain: a systematic review and meta-analysis. JAMA Oncol 2019;6:271–8.
[16] Anshasi Huda A, Ahmad M. An assessment of methodological quality of systematic reviews of acupuncture and related therapies for cancer-related pain. Complement Ther Clin Pract 2018;32:163–8.
[17] Chiu HY, Hyse YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. Eur J Cancer Care (Engl) 2017;26:1–17.
[18] Paley CA, Johnson MI, Tasmani OA, Bagnall AM. Acupuncture for cancer pain in adults. Cochrane Database Syst Rev 2011;CD007753.
[19] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[20] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines? Adult cancer pain Version 2.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. 2017
[21] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[22] Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9:e99682.

[23] Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[24] Veroniki AA, Vasiliadis HS, Higgins JPT, et al. Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013; 42:332–45.

[25] Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment metaanalysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.

[26] Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[27] Bom Pedro RD, Rachinger H. A kinked meta-regression model for publication bias correction. Res Synth Methods 2019;10: 497–514.