Acupuncture in oncological pain relief: A systematic review of randomized clinical trials

Acupuntura no alívio da dor oncológica: revisão sistemática de ensaios clínicos randomizados

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Abstract

Introduction: Cancer pain has a considerable impact on patients' health and quality of life, and its treatment is essentially based on opioid use. **Objective:** To report the effectiveness of acupuncture in relieving cancer pain (secondary to the disease or to the corresponding therapy) or in decreasing opioid use compared to other interventions. **Methods:** A systematic review of randomized clinical trials was conducted following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. The trials were selected from the PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. **Results:** The search strategy resulted in the inclusion of eight trials, of which five compared acupuncture and drug therapy and three compared acupuncture and placebo. Seven trials reported decreased pain and analgesic use. The trials showed clinical heterogeneity, making a meta-analysis unfeasible. **Conclusion:** The findings herein provided no robust evidence to support the routine use of acupuncture as an adjuvant therapy in the treatment of cancer pain. However, its use is promising since the results showed a trend toward decreased pain and analgesic use, thus justifying further studies in the future.

Keywords: Acupuncture. Cancer pain. Complementary therapies. Evidence-based clinical practice.

Resumo

Introdução: *A dor oncológica implica em elevado impacto à saúde e qualidade de vida dos pacientes, sendo o tratamento baseado fundamentalmente no uso de opioides.* ***Objetivo:*** *Relatar a efetividade da acupuntura no tratamento da dor oncológica (secundária à doença ou ao seu tratamento) para o alívio do quadro álgico ou redução do consumo de opioides em comparação a outras intervenções.* ***Métodos:*** *Revisão sistemática de ensaios clínicos randomizados orientada pelas recomendações do Cochrane Handbook for Systematic Reviews of Interventions. Foram selecionados estudos obtidos na Pubmed, Web of Science e CENTRAL.* ***Resultados:*** *A estratégia de busca resultou na inclusão de oito estudos, dos quais cinco compararam acupuntura e terapia farmacológica, enquanto três compararam acupuntura e placebo. Observou-se redução da dor e do consumo de analgésicos em sete estudos. Os ensaios apresentaram heterogeneidade clínica, inviabilizando a realização de metanálise.* ***Conclusão:*** *Os achados obtidos não fornecem evidências robustas para sustentar a utilização rotineira da acupuntura enquanto terapia adjuvante no tratamento da dor oncológica. Sua utilização, no entanto, é promissora, uma vez que os resultados apontaram uma tendência na redução da dor e no consumo de analgésicos, justificando, assim, a condução de novos estudos.*

Palavras-chave: *Acupuntura. Dor oncológica. Terapias complementares. Prática clínica baseada em evidências.*

Introduction

Cancer pain is one of the main symptoms in patients with advanced cancer; it is mainly caused by tumor growth, soft tissue or adjacent structure infiltration, nerve compression or as a consequence of therapeutic modalities of cancer control and treatment, such as surgical interventions, chemotherapy, and radiotherapy,[1] eventually becoming a long-term sequelae of cancer treatment.[2]

The high prevalence of this cancer pain is a global health concern. About 40% of newly diagnosed or intermediate-stage cancer patients and 90% of advanced cancer patients present moderate to severe pain.[3] Despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients.[4]

The first-line treatment for cancer pain involves the administration of opioid analgesics; however, this intervention can result in side effects, such as sedation, respiratory depression, constipation, and nausea, which negatively affect the patient's quality of life.[1,5] Furthermore, long-term opioid use can lead to opioid dependence owing to the high doses prescribed, which consequently increases the risk of death due to overdose.[6] In this scenario, integrative oncology becomes notable in its use of complementary treatments, rather than conventional therapies, to alleviate disease symptoms and cancer therapy-related side effects and consequently improve patients' well-being and quality of life.[7]

Integrative oncology includes elements of traditional Chinese medicine. Of the complementary therapeutic alternatives included in integrative oncology, acupuncture has been widely used to control a variety of cancer-related symptoms and conditions, and disease treatment-related adverse effects.[8]

Acupuncture refers to a group of therapeutic techniques characterized by the insertion of needles into specific points on the skin (acupuncture points), sometimes followed by manual manipulation or electrical stimulation.[9] These needles regulate endogenous opioid, serotonin, and norepinephrine levels, inhibit visceral nociceptors and inflammatory cytokines, and stimulate the central nervous system.[10]

The high incidence of cancer and the increased survival of patients presuppose new care strategies for symptoms related to the disease or induced by treatments and for patients needing palliative actions to improve their quality of life. In this perspective, acupuncture can be considered a complementary form of treatment, especially for clinical concerns with limited conventional treatment alternatives.[11]

Therefore, this study aimed to report the effectiveness of acupuncture in relieving cancer pain (secondary to the disease or to its therapy) or in reducing opioid use compared to other interventions.

Methods

This is a systematic review of randomized clinical trials following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, version 6.0,[12] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines.[13] The review was filed in the International Prospective Register of Systematic Reviews (PROSPERO), under registration no. CRD42018111689.

The PICO acronym was used to elaborate the research question. The guiding question was: "What is the effectiveness of acupuncture in the treatment of cancer pain (secondary to the disease and/or to its therapy) regarding pain symptom and analgesic use reduction on comparing different acupuncture techniques, acupuncture points, Sham acupuncture, and pharmacological therapy?"

The location and selection of primary studies that answered the research question required a rigorous search strategy, resulting in a comprehensive, complete, objective, and reproducible selection of studies to avoid the risk of bias or non-inclusion of relevant studies. The study considered randomized clinical trials evaluating the use of acupuncture as a strategy for relieving cancer pain secondary to the disease or to the therapy compared to the use of other control strategies (pharmacological or not).

There were no restrictions on publication date or language (except studies available only in Mandarin). Studies with other methodological designs or that described the use of acupuncture in other diseases or symptoms were excluded.

A comprehensive literature search was conducted between January and April 2020 in the MEDLINE/PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) international databases using the Medical Subject Headings terms (MeSH Terms) "cancer pain" and "acupuncture." Synonyms, combinations of the terms with the Boolean operators "AND" and "OR," and the use of truncation symbols "*" (Cochrane and PubMed) and "$" (Web of Science) were also considered (Table 1).

In addition, the gray literature was searched to identify relevant reports, including government reports, dissertations, theses, and abstracts published in conference proceedings and in the ClinicalTrials.gov (US National Library of Medicine) database. Reference lists of retrieved randomized clinical trials were also investigated to identify potentially eligible studies that were not found using the aforementioned search strategy.

All retrieved studies were screened and evaluated for eligibility according to the inclusion criteria by two independent reviewers. The screening and selection process included two phases: (i) evaluation of the titles and abstracts of all identified studies; (ii) full reading of selected studies and justification for exclusions. The level of agreement between reviewers regarding the inclusion or exclusion of studies was determined by the Kappa measurement.

The data obtained were organized for presentation in a narrative synthesis, including authorship and year of publication; country of origin; title of the manuscript and journal; and clinical information, including number of participants, intervention and comparison groups, time, and main outcomes. Critical analysis of the included studies was performed using the Cochrane Risk of Bias Tool for risk of bias assessment available in the Review Manager version 5.3 software.[14]

Table 1 - Search strategy and databases

| Databases	Descriptors
Pubmed/ MEDLINE	(((((((((acupuncture[Title/Abstract] OR "acupuncture"[All Fields]) OR "acupuncture therapy"[Title/Abstract] OR "acupuncture therapy"[All Fields]) OR electroacupuncture[Title/Abstract]) OR "electroacupuncture"[All Fields]) OR "acupuncture points"[Title/Abstract] OR "acupuncture points"[All Fields]) OR acupoint*[Title/Abstract]) OR acupoint*[All Fields]) OR auriculotherapy[Title/Abstract]) OR "auriculotherapy"[All Fields]) OR "intradermal acupuncture"[Title/Abstract]) OR "intradermal acupuncture"[All Fields]) AND "cancer pain"[Title/Abstract] OR "cancer pain"[All Fields]) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
Web of Science	((acupuncture OR "acupuncture therapy" OR electroacupuncture OR "acupuncture points" OR acupoint OR auriculotherapy OR "intradermal acupuncture" AND "cancer pain")) AND TÓPICO: (("clinical trial"))
Cochrane Central	SEARCH #1: (acupuncture):ti,ab,kw SEARCH #2: ("acupuncture therapy"):ti,ab,kw SEARCH #3: (electroacupunture):ti,ab,kw SEARCH #4: ("acupuncture points"):ti,ab,kw SEARCH #5: (acupoint):ti,ab,kw SEARCH #6: (auriculotherapy):ti,ab,kw SEARCH #7: ("intradermal acupuncture"):ti,ab,kw SEARCH #8: ("cancer pain"):ti,ab,kw SEARCH #9: (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND #8

The studies were judged by two reviewers according to the categories of low risk of bias, high risk of bias, and undetermined risk of bias for the following domains: generation of sample randomization by allocation sequence (selection bias), blinding of participants and researchers (performance bias), blinding of outcome evaluators (detection bias), incomplete outcomes (attrition bias), and selective reporting of outcomes (reporting bias). The level of agreement between reviewers was determined by the Kappa index, and disagreements were resolved by a third reviewer.

All clinical trials included were categorized through the allocation secrecy described in the Cochrane handbook as: category A (appropriately described allocation process); category B (allocation process not clearly described, but the study points to randomization); category C (allocation confidentiality inadequately conducted, e.g., order of arrival, medical record number, and date of birth); and category D (participant randomization was not evidenced).

Additionally, the STRICTA checklist (Standards for Reporting Interventions in Clinical Trials of Acupuncture) was administered as an instrument that sets standards for reporting clinical trials that include acupuncture as an intervention. The checklist includes items on the justification for acupuncture, needling details, treatment regimen, other treatment components, practitioner history, and control or comparator interventions.15 Studies published before 2010, the year of the publication of STRICTA, were not considered in this evaluation stage. The authors declare no conflicts of interest or funding sources for the preparation and conduct of this systematic review.

Results

The search strategy resulted in the retrieval of 1,205 studies (Figure 1). The Kappa agreement index was 0.829 (p < 0.001).
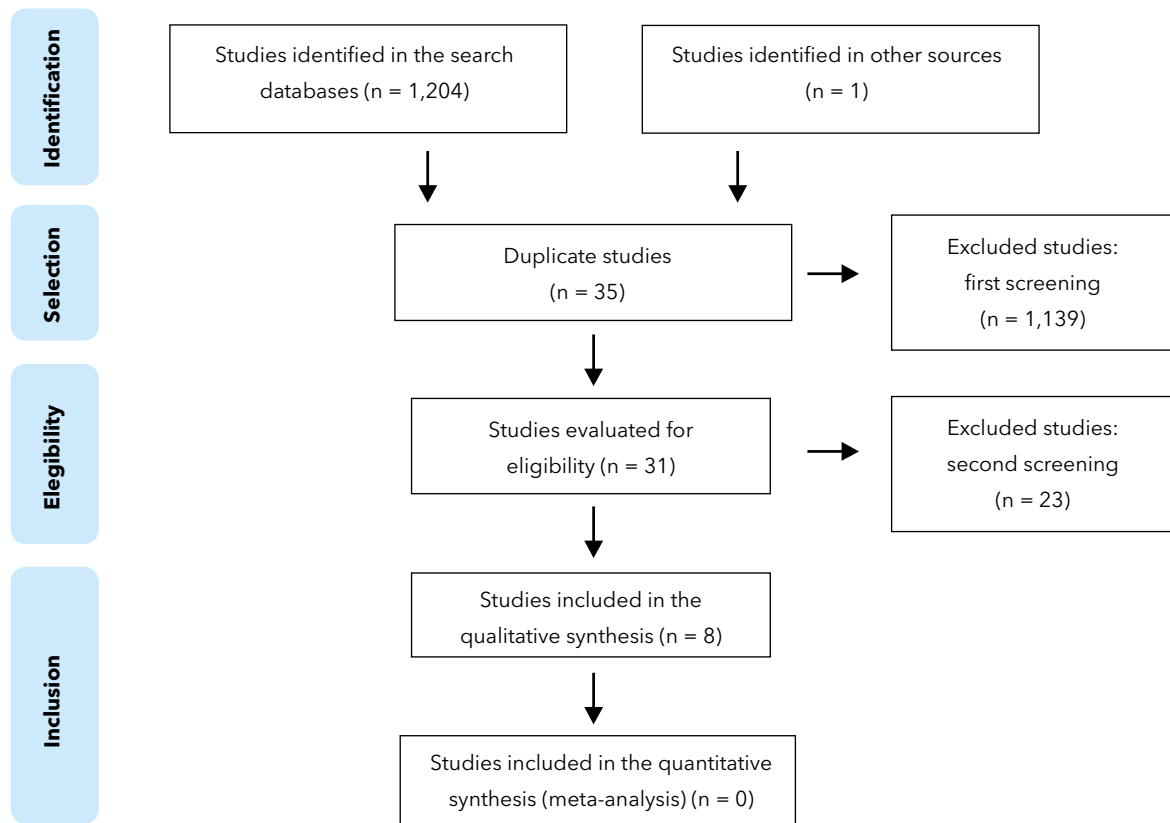
Figure 1 - PRISMA flowchart of identification, selection, eligibility, and inclusion of clinical trials. Review Manager 5.3, 2021.

Some of the highlighted reasons for exclusion in the second screening were as follows: use of other integrative practices (n = 6), effects of acupuncture on quality of life (n = 1), prevention of chemotherapy-induced worsening of peripheral neuropathy (n = 1), studies that did not delimit cancer pain (n = 3), studies unavailable in full (n = 8), studies available only in Mandarin (n = 2), and ongoing studies (n = 2).

The internal validation of the eight included studies[16-23] included risk of bias assessment for the selection, performance, detection, attrition, and reporting domains. The domains were classified as "low risk of bias," "high risk of bias," and "undetermined risk of bias" (Figure 2). The inter-rater agreement (Kappa) for the individual classification of fields was 0.623 (p < 0.001, CI95%).
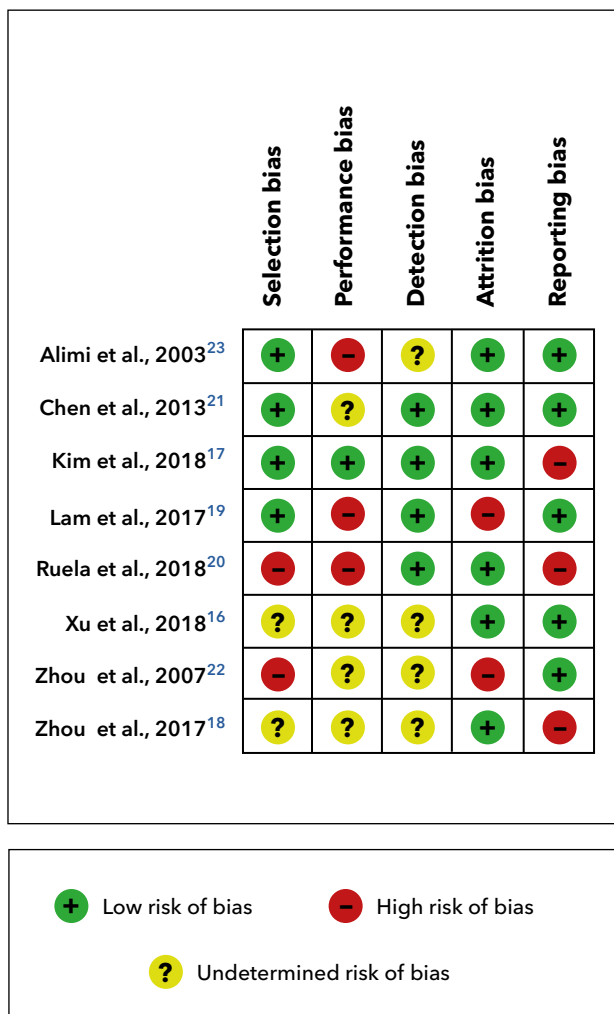

Figure 2 - Bias risk summary. Review Manager 5.3, 2021.

Two studies presented a high risk of selection bias owing to the use of not-recommended allocation methods, biased currency[20] and simple envelope.[22] Two other studies were classified as having an indeterminate risk of selection bias for mentioning randomization but not describing the process.[16,18]

Only one study blinded participants and professionals using needles and placebo needles.[17] The other trials presented a high or indeterminate risk of performance bias owing to the clinical heterogeneity between interventions and comparators.

In the domain "detection bias," 50% of the studies did not explain the evaluators' blinding and were therefore categorized as having an undetermined risk of bias.[16,18,22,23]

Two studies were judged as being at high risk for "segment bias." One of them had significant segment losses in the treatment and control groups that resulted in statistical heterogeneity,[19] while the other disproportionately distributed the participants into the intervention and control groups.[22]

Although no selective reporting of results was identified, three studies received funding and were classified as having a high risk of reporting bias.[17,18,20]

In the critical assessment of allocation confidentiality, four studies were classified as category A,[17,19,21,23] for adequately describing the allocation process; two as category B[18,22] for mentioning the participant randomization process; and two as category C[16,20] for inappropriately allocating the participants. No studies were classified as category D. Tables 2 and 3 summarize the results of the included studies.

Of the eight studies included, three compared acupuncture with different pharmacological strategies for the treatment of cancer pain;[16,18,22] two of these three studies reported reduced pain intensity and/or decreased analgesic use. Only one study showed no statistical differences benefiting the intervention.[16]

The remaining five studies compared different acupuncture techniques without pharmacological agent combinations.[17,19,20,21,23] All of them presented reduced pain intensity in the treatment groups compared to the placebo groups.

In the included studies, the analgesic efficacy of acupuncture was measured using the numerical rating scale,[17,19,20-22] visual analog scale,[16,23] and the World Health Organization scale for assessing quality of life (WHOQOL-100 Quality of Life Assessment Scale).[18]

The eight studies that were included showed clinical heterogeneity regarding different acupuncture techniques (electroacupuncture, intradermal acupuncture, auriculotherapy); the use of acupuncture alone or in combination with pharmacological therapy; the use of multiple acupuncture points; and varying etiologies of cancer pain, making a meta-analysis unfeasible.

As for the recommended standards for reporting clinical trials that use acupuncture as an intervention, only one of the studies declared the use of the STRICTA checklist.[19]

Five clinical trials investigated the Traditional Chinese Acupuncture,[16,18-21] while one study analyzed the Korean Traditional Acupuncture.[17] All studies supported the use of acupuncture and its practice. Three studies reported the qi (vital energy) as a type of response sought in sessions.[19-21]

About needling, all studies described the characteristics of the needles. Two studies did not cite the number of needle insertions per participant per session.[17,21] All studies described the names of the acupuncture points or their respective anatomical location. There was no mention of the use of interventions concomitant with acupuncture. Only one study did not describe the number of insertions per participant.[17] All studies mentioned treatment session frequency and duration. As for the practitioners' background, three studies did not report their professional certification and qualification.[16,18,21]

All studies adequately described the interventions performed in the comparison group, but only two studies adequately oriented patients about the procedure.[17,20] Only one study reported significant treatment variations over segment time.[19]

There were inconsistencies in acupuncture treatment protocols described in the clinical trials, with variable point selection, needle number, insertion depth, needle manipulation and stimulation, presence or absence of needle sensation (qi), and number and duration of the sessions.

Table 2 - Narrative synthesis and general data of the studies

Authors/Year	Country	Title	Journal/Database
Alimi et al., 2003[23]	France	Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial	Journal of Clinical Oncology/Pubmed
Zhou et al., 2007[22]	China	Acupuncture plus three-step analgesic ladder principle for cancer pain relief: Clinical observation on 24 cases	Journal of Acupuncture and Tuina Science/ Grey literature
Chen et al., 2013[21]	China	Electroacupuncture treatment for pancreatic cancer pain: A randomized controlled trial	Pancreatology Pubmed
Lam et al., 2017[19]	China	A pilot randomized controlled trial of acupuncture at the Si Guan Xue for cancer pain	BMC Complementary Medicine and Therapies/ Pubmed
Zhou et al., 2017[18]	China	The effect of acupuncture on chemotherapy-associated gastrointestinal symptoms in gastric cancer	Current Oncology/Pubmed
Kim et al., 2018[17]	South Korea	Intradermal acupuncture along with analgesics for pain control in advanced cancer cases: A pilot, randomized, patient-assessor-blinded, controlled trial	Integrative Cancer Therapies/Pubmed
Ruela et al., 2018[20]	Brazil	Effectiveness of auricular acupuncture in the treatment of cancer pain: randomized clinical trial	Revista da Escola de Enfermagem da USP/ Pubmed
Xu et al., 2018[16]	China	Clinical analysis of electroacupuncture and multiple acupoint stimulation in relieving cancer pain in patients with advanced hepatocellular carcinoma	Journal of Cancer Research and Therapeutic/Pubmed

Table 3 - Study distribution by number of participants, intervention and control groups, and main outcomes

Study	Intervention (n)	Comparison (n)	Main outcomes
Alimi et al., 2003[23]	Three different arms Arm 1 (Intervention - Auricular acupuncture - points selected individually for each patient, n = 28).	Arm 2 (Control group 1 - Ear acupuncture at placebo points - ineffective acupuncture, n = 23); Arm 3 (Control group 2 - Seeds fixed in placebo points, n = 28).	Pain intensity decreased by 36% after two months compared to baseline in the intervention group, and there was a slight change for patients receiving placebo (2%). Difference: p < 0.0001. Pain scores on D30 were also lower in the intervention group (Mean ± SD, 44 ± 19) than in the Control 1 (Mean ± SD, 54 ± 25) or Control 2 (Mean ± SD, 56 ± 19) groups.
Zhou et al., 2007[22]	Acupuncture (daily sessions) combined with three-step analgesic ladder approach (n = 24). Application in points corresponding to the location of pain.	Three-step analgesic stair approach (n = 12)	The total effective rate and marked effect rate of the intervention group were 87.5% and 54.2%, respectively, while those of the control group were 66.7% and 25%, respectively, indicating a statistical difference (p < 0, 05) in terms of therapeutic efficacy.
Chen et al., 2013[21]	Intervention Group Electroacupuncture (n = 30)	Placebo group (Sham) (n = 30)	In the intervention group, pain intensity decreased after 3 sessions compared to baseline (1.67; CI95%, 1.46 - 1.87). The Sham group presented minor pain reduction between the three sessions (0.13; CI95%, 0.08 - 0.35). Differences between the two groups: p < 0.001.
Lam et al., 2017[19]	Three different arms with seven treatment sessions: Arm 1 (Si Guan Xue, n = 12)	Arm 2 (Si Guan Xue combined with the most commonly used acupuncture points, n = 9); Control Arm (most commonly used acupuncture points, n = 9).	Pain reduction was more prominent on day 5 in Arm 2 than in the Control Arm (p < 0.05). There were no differences in pain score among the three groups (p > 0.05). No serious adverse events were observed.
Zhou et al., 2017[18]	Standard chemotherapy (Oxaliplatin-Paclitaxel) + acupuncture (n = 28)	Standard chemotherapy (Oxaliplatin-Paclitaxel) (n = 28)	Pain persisted for 7 (± 2) minutes in the intervention group and for 16 (± 5) minutes in the control group. Compared with the control group, the experimental group showed decreased pain frequency or duration (p < 0.05).
Kim et al., 2018[17]	Intradermal acupuncture (n = 14)	Sham acupuncture (n = 13)	In the intervention group, 64.3% of patients (9/14) reported reduced analgesic use compared to 38.5% (5/13) in the Sham group (p = 0.180). Self-reported pain level decreased after treatment (-1.54 ± 1.45 and -1.15 ± 1.57), at the first follow-up consultation (-1.57 ± 2.06 and -1.54 ± 1.20) and at the end of the follow-up period (-1.00 ± 2.22 and -1.08 ± 1.38) in the intervention and control groups, respectively (p < 0.001).
Ruela et al., 2018[20]	Ear acupuncture (in energy balance points and in points indicated for pain treatment) (n = 11)	Placebo group: Auricular acupuncture (placebo fixed points) (n = 12)	There were differences between groups regarding the reduction of pain intensity (p < 0.001) and of analgesic use (p < 0.05). There were significant differences in daily analgesic doses (p = 0.010) and in the amount of analgesics used (p = 0.019).
Xu et al., 2018[16]	Electroacupuncture (stimulation of multiple acupuncture points) (n = 32)	Fentanyl transdermal patch. (n = 33)	The pain score of the intervention group significantly decreased on day 3 (p < 0.05), but the pain scores were not different (p > 0.05) four days after treatment. The incidence of adverse reactions in the two groups was 9.4% and 12.1%, respectively (p > 0.05).

Discussion

The objective of this systematic review was to evaluate the effectiveness of different acupuncture techniques as an adjuvant cancer-pain treatment compared to other pain-control alternatives. In is context, 376 patients were analyzed in eight randomized clinical trials, randomly distributed to investigate the outcomes of reduced pain experience and decreased analgesic use.

Several similar systematic reviews have evaluated the effects of acupuncture in relieving pain induced by cancer of multiple etiologies or cancer therapy (chemotherapy, radiotherapy, cancer surgery, and hormonal therapy). Their results showed that acupuncture was not better than conventional medicine in relieving cancer pain in adults, and the quality of evidence was considered moderate.[15,24-26]

Nonetheless, a meta-analysis of 29 randomized clinical trials selected from international and Chinese databases showed better results with acupuncture for pain relief in subgroups for the presence of malignancy and surgery-induced pain. The researchers suggested that acupuncture should be used as part of a multimodal approach to reduce cancer-related pain.[27]

Another similar study reported that acupuncture and related therapies significantly reduced pain compared to the standard treatment (controlled-release morphine sulfate tablets), also suggesting that the intervention had a significantly shorter analgesic onset time compared to conventional therapy.[9]

In the context of palliative cancer care, a retrospective study analyzed the medical records of 68 patients and showed that acupuncture improved pain and other symptoms, such as depression and fatigue, and that patients with higher baseline pain indices and advanced disease were more likely to experience pain reduction.[28]

As an adjuvant treatment, acupuncture may increase the duration of the analgesic effect of conventional pharmacological therapy in patients with advanced cancer. A comparison of the isolated use of morphine and the combination of morphine and acupuncture showed a 7-hour increase in the duration of analgesic effects.[29] Therefore, acupuncture can be recommended as a complementary therapy, if cancer pain is poorly controlled with conventional alternatives.[30]

The number of acupuncture sessions, needling depth, acupuncture manipulation, and needle retention time varied widely among the included studies. In traditional acupuncture, the intervention is not standardized and can be adjusted according to each patient's syndrome (Zheng).[31] Acupuncture is a complex intervention wherein treatment regimens are followed according to individual needs and responses, which are usually identified based on the practitioner's experience.

Complications are rare in acupuncture, making it safe for the management of pain in cancer patients. Some of the included studies reported adverse effects in participants receiving acupuncture, such as subcutaneous bleeding,[16] pain at the acupuncture site for three days,[19] acupuncture point bruises[20] and fatigue.[17] No severe adverse events were reported. These data are corroborated by a German study with 97,733 patients (over 760,000 sessions) that reported only six cases of potentially severe adverse events, including depression, hypertensive crisis, vasovagal reaction, asthma attack, and pneumothorax.[32]

Complementary integrative therapies meet the growing demands of patients with cancer-related pain and should be considered along with pharmaceutical and/or interventional therapies.[33] The evidence-based integration of acupuncture and analgesic use, guided by the patient's treatment preferences, represents an essential aspect of patient-centered care and has the potential to address unmet needs for cancer pain management.[34]

Conclusion

Although the use of different acupuncture techniques is associated with reduced cancer pain and decreased analgesic use, this study found no robust evidence to support the routine use of acupuncture as an adjuvant therapy in the treatment of cancer pain. The low methodological quality and inadequate sample sizes of the clinical trials included and the impossibility of synthesizing and grading evidence from different types of studies owing to clinical heterogeneity corroborate the study's results. These results may have some limitations owing to the impossibility of accessing studies published only in Chinese databases or written in Mandarin, as well as the diversity of techniques used in the studies.

The use of acupuncture to relieve cancer-related pain appears to be promising owing to a demonstrated trend toward reducing pain and analgesic use. Thus,

better-designed clinical studies focused on short-term and long-term therapeutic and economic impact are needed to determine the inclusion of this integrative practice as an alternative or adjuvant therapy in the context of cancer pain control, in order to ensure individualized and effective analgesia regimens.

Furthermore, use of the STRICTA checklist is recommended to describe treatment protocols to increase the reproducibility of methods used in clinical trials that include acupuncture as an intervention.

Authors' contribution

MMD: research project design, general orientation, manuscript writing, third reviewer, and PROSPERO registry filing. CMT: manuscript writing, first reviewer, search strategy development and execution. PKH: review and final writing, grey literature analysis, translation, and manuscript collection. JLSA: manuscript writing, second reviewer, search strategy development and execution. CKLC: methodological support with the Cochrane handbook, PRISMA, Review Manager software, and risk of bias tool. SOI: review and final writing, academic support.

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