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META-ANALYSIS

The Efficacy of Acupuncture in the Treatment of Chemotherapy-Induced Peripheral Neuropathy: A Network Meta-Analysis

Teng Zhang, MB; Qiang Zhang, MB; Peiye Zhu, MB; Weidong Sun, MB; Zaiqiao Ding, MM; Lu Hu, MM

ABSTRACT

Background • Chemotherapy-induced peripheral neuropathy (CIPN), one of the most common adverse events associated with chemotherapy, may affect efficacy because of the interruption of chemotherapy or change of regimen in severe cases, and may even increase cancer mortality. Relevant data supports the evidence that acupuncture can treat pain and sensory abnormalities. However, choosing the most effective acupuncture therapy is difficult because of the lack of evidence-based medicine and comparisons between different acupuncture therapies for treating CIPN. The aim of this study was to use a network meta-analysis (NMA) to evaluate the efficacy of different acupuncture therapies for CIPN.

Methods • We searched Embase, PubMed, Web of Science, The Cochrane Library, The Chinese Journal Full Text Database, Chinese Biomedical Literature Database, and WanFang Database for randomized controlled trials (RCTs) of acupuncture for CIPN. The search period was from the creation of the relevant library to August 10, 2023. A total of 2 investigators independently performed literature screening, data extraction, and risk for bias evaluation. Stata 14.0 software (StataCorp LLC, College Station, Texas USA), was used for the NMA.

Results • A total of 13 eligible RCTs involving 746 patients and 6 acupuncture therapies were included in the study. The NMA results showed that electroacupuncture was superior to moxibustion, manual acupuncture, acupoint injection and Western medicine in improving the total effective rate of treatment of CIPN; electroacupuncture + moxibustion was better than manual acupuncture, acupoint injection, and Western medicine. Manual acupuncture's total effective rate was better than Western medicine. However, electroacupuncture was the most effective treatment for CIPN according to the surface under the cumulative ranking curve (SUCRA) ranking.

Conclusion • After a comprehensive evaluation of 6 acupuncture therapies for treating CIPN based on NMA, electroacupuncture may be the best option for treating CIPN. However, would be more convincing to get evidence from more RCTs. (*Altern Ther Health Med.* 2023;29(8):898-906).

Teng Zhang, MB; Weidong Sun, MB; Department of Clinical Medicine; Dazhou Vocational and Technical College; Dazhou, Sichuan Province, China. **Qiang Zhang, MB; Zaiqiao Ding, MM; Lu Hu, MM;** Department of Oncology; Army Medical Center of PLA; Chongqing, China. **Peiye Zhu, MB;** College of Pharmacy and Bioengineering; Chongqing University of Technology; Chongqing, China.

Corresponding author: Lu Hu, MM
E-mail: hulumeier2023@163.com
Corresponding author: Zaiqiao Ding, MM
E-mail: dingzaiqiao@163.com

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN), a common adverse event with chemotherapy treatment in patients with malignant tumors, manifests as severe sensory, motor and autonomic nerve damage and dysfunction.[1,2] Multiple chemotherapy drugs and their severity can positively cause CIPN depending on the dose[3]; this is especially true with platinum and paclitaxel.[4] These nerve injuries mainly occur in the dorsal root ganglion, which means the neuropathy is primarily sensory, with lesser involvement of the motor and autonomic nerves.[5] A large sample meta-analysis by Seretny, et al[6] showed that the prevalence of CIPN at 1, 3 and 6 months or longer after chemotherapy was 68.1%, 60.0% and 30.0%, respectively. This disease can have a significant impact on a patient's quality of life (QoL) by limiting their ability to undergo chemotherapy or even forcing them to end treatment early due to intolerance.

According to the latest 2020 clinical practice guidelines for CIPN from the American Society of Clinical Oncology (ASCO®) and the European Society for Medical Oncology (ESMO), there are no recommended drugs for the prevention of CIPN.[7,8] ASCO guidelines recommend duloxetine as a

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clinical agent in patients with diagnosed CIPN, but there is limited supporting evidence for this treatment.[7,9,10] In addition, the adverse events associated with medications, such as nausea, dry mouth, constipation, diarrhea, vomiting and more, can reduce the efficacy of treatment and further diminish patient QoL.[11]

Acupuncture, a Traditional Chinese Medicine (TCM) therapy with remarkable efficacy and associated with few adverse events, has achieved positive results in treating peripheral neuropathy stemming from various causes.[12-16] Acupuncture is recommended as a complementary alternative therapy for managing cancer pain and peripheral neuropathy by relevant evidence-based clinical practice guidelines.[17] Unfortunately, there are few studies on the use of acupuncture for treating CIPN in China or abroad. Although several meta-analyses have shown that acupuncture is effective in treating CIPN, it is uncertain which acupuncture therapy option is most effective.[18-20] Therefore, this study systematically compared the efficacy of different acupuncture therapies for CIPN using the Network Meta-Analysis (NMA) method to provide a basis for complementary and alternative therapies in clinical practice.

METHODS

This NMA was reported as following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-extension statement for network meta-analysis (PRISMA-NMA)[21] (Table S1). The protocol for the review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42023448604).

Inclusion and Exclusion Criteria

Types of included studies. Only randomized controlled trials (RCTs) were included in this NMA.

Participants. Patients diagnosed with CIPN.

Exclusion Criteria. (1) Non-RCTs; (2) Studies with treatment methods other than acupuncture were included in the experimental group; (3) Studies without before and after controls; (4) Duplicate published studies.

Interventions and Comparisons

The experimental group was treated with the following therapies: manual acupuncture, electroacupuncture, moxibustion, warm acupuncture, etc. Western medicine treatments included vitamin B, mecobalamine, neurotropin, etc. The control group received Western medicine, sham or other treatments.

Outcomes

(1) Total effective rate
(2) Nerve conduction velocity
(3) Nerve conduction amplitude
(4) Pain score

Search Strategy

We searched Embase, PubMed, Web of Science, The Cochrane Library, The Chinese Journal Full Text Database, Chinese Biomedical Literature Database, and WanFang Database for RCTs of acupuncture for CIPN. The search timeframe was from relevant library creation to August 10, 2023. The search terms included acupuncture, electroacupuncture, moxibustion, warm acupuncture and moxibustion, chemotherapy-induced peripheral neuropathy, etc. The detailed search strategy for the PubMed database is provided in the supplementary material (Table S2).

Data Extraction

A total of 2 experts thoroughly reviewed the literature, gathering relevant information and cross-referencing their findings. If there were any disagreements, an impartial 3rd party was consulted to resolve them. The study investigators were also contacted to provide any additional details that needed to be included. The screening process involved evaluating the title and abstract first, then reading the full text to determine whether it was relevant.

The data extraction process involved gathering the following:

- Basic information about the study, such as the title, author, date and publication
- Characteristics of the study population, including age and sample size
- Details of the intervention, such as the type and timing
- Key factors affecting the evaluation of any risk for bias
- Outcome indicators, measurements and data collected during the study

Quality Assessment

The included studies were evaluated for bias by 2 independent investigators who cross-checked their results. The RCT risk for bias assessment tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0[22] was used to assess the risk for bias. The evaluation entries for the included RCTs followed the categories of selection bias, implementation bias, measurement bias, follow-up bias, reporting bias and other biases.

Data Analysis

In this study, 2 different methods were used to measure the effectiveness of interventions: risk ratios (RR) for count data and standardized mean differences (SMD) for measured data. The results were analyzed with a 95% CI, and study heterogeneity was determined using the Q test and I^2 value. If $P > .1$ and $I^2 < 50\%$, the studies were considered homogeneous, and a fixed-effects model was applied. Otherwise, a random-effects model was used. Subgroup analysis was performed based on the duration of the intervention (>2 weeks vs ≤2 weeks), and sensitivity analysis was used to check the stability of the results. The node-splitting method was applied to test whether there was inconsistency between direct and indirect comparison results. If $P > .05$, the results of direct and indirect comparisons were considered consistent.[23] The surface under the

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cumulative ranking curve (SUCRA) was used to rank cumulative ranking probability. Interventions were ranked according to the magnitude of SUCRA values, with larger values indicating more benefit from the intervention. A "corrected-comparison" funnel plot was used to evaluate whether there was a small sample effect or publication bias. Stata 14.0 (Stata Corp LLC, College Station, Texas USA) and RevMan 5.3 (Cochrane, https://revman.cochrane.org/info) software were used for direct comparative meta-analysis, NMA and graph plotting.

RESULTS

Literature Screening Result

Out of 2468 documents found, 482 duplicates were excluded during the initial review, 1945 publications were removed after reading the title and abstracts of the remaining publications and 28 were excluded after reading the full text. A total of 13 RCTs,[24-36] including 6 acupuncture therapies, were included for the final meta-analysis (Figure 1).

Basic Characteristics of Included Studies

A total of 13 RCTs,[24-36] with 746 patients, were involved in this meta-analysis. The study focused on 6 different acupuncture therapies, which included manual acupuncture, electroacupuncture, acupoint injection, moxibustion, warm acupuncture and moxibustion and electroacupuncture + moxibustion. Most of the studies were conducted in China; one was a 3-arm study split into 3 separate trials. The drugs utilized in the study were B vitamins, mecobalamine and neurotropin. The duration of the intervention in the trials ranged from 2 to 6 weeks. The basic characteristics of the studies included are shown in Table 1.

Risk for Bias Assessment

Figure 2 displays the results of the risk for bias assessment. Of the 9 RCTs evaluated, the randomization process was considered low-risk in all except 1 RCT, which was assessed as high- risk; the randomization method for the remaining RCTs needed clarification. Regarding allocation concealment, 3 RCTs were deemed low-risk, while the rest were unclear. Only 1 RCT was blinded, and the rest were unclear. For incomplete data, selective reporting bias and other sources of bias for all RCTs showed low-risk bias.

Directly Compared Meta-analysis Results

A total of 6 RCTs reported the total effective rate of manual acupuncture compared with Western medicine for CIPN. After analyzing the results, we found that manual acupuncture was more effective than Western medicine (risk ratio [RR] = 1.45; 95% CI, 1.12-1.87; P = .004) (Figure 3).

Only 1 study was available for comparison of other acupuncture therapies with Western medicine for CIPN and to measure the total effective rate, nerve conduction velocity, nerve conduction wave amplitude and pain score. Therefore, a descriptive analysis was conducted, and the results are available in the supplementary material (Table S3).

Figure 1. Flowchart of the literature screening process.

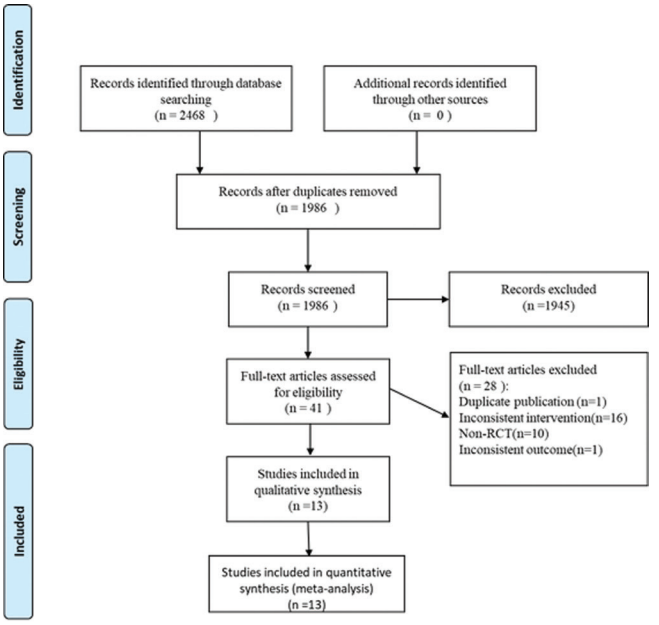
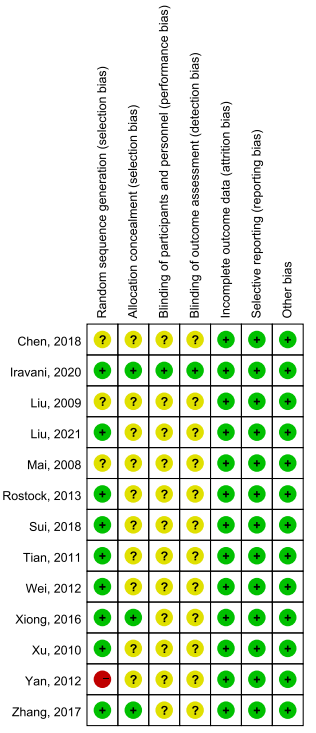


Figure 2. Risk for bias graph of the included RCTs.



After performing a descriptive analysis, we found that there was a statistically significant difference in total response rates between electroacupuncture + moxibustion and Western medicine, manual acupuncture and electroacupuncture and moxibustion and Western medicine (P < .05). However, there was no significant difference between acupoint injection and Western medicine, manual acupuncture and acupoint injection, and warm acupuncture and moxibustion and Western medicine (P > .05).

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Table 1. Characteristics of interventions of included studies

Included studies	Stata	Sample size		Age		Interventions		No. of Patients (Start)	No. of Patients (End)	Treatment course (week)
		T	C	T	C	Intervention of treatment	Intervention of control			
Liu, 2021	China	30	30	48.7±8.7	47.9±7.9	Moxibustion	Mecobalamine	60	60	4
Rostock,2013	Germany	14	15	49.9 ± 9.6	56.3 ±11.1	Electroacupuncture	Vitamin B1/B6	29	29	3
Zhang, 2017	China	19	19	37-78	36-79	Manual acupuncture	Electroacupuncture	38	37	6
Sui, 2018	China	10	10	59.10±7.62	57.7±8.33	Electroacupuncture	Mecobalamine	20	20	3
Wei, 2012	China	30	30	33-74	33-74	Electroacupuncture + Moxibustion	Mecobalamine	60	60	6
Tian, 2011	China	38	38	33-71	29-69	Warm acupunctrue	Neurotropin	76	76	3
Xiong, 2016	China	30	30	58.3±10.4	56.9±10.2	Manual acupuncture	Mecobalamine	60	58	4
		30	30	59.7±12.0	56.9±10.2	Acupoint injection	Mecobalamine	60	59	4
		30	30	58.3±10.4	59.7±12.0	Manual acupuncture	Acupoint injection	60	57	4
Iravani,2020	Iran, China	19	19	57.95±10.39	58.79±8.36	Manual acupuncture	Vitamin B1+Gabapentin	38	38	4
Chen,2018	China	40	40	49.02±8.63	48.75±8.67	Manual acupuncture	Mecobalamine	80	80	2
Mai, 2008	China	30	30	25-72	25-72	Manual acupuncture	Vitamin B1+Vitamin B12	60	60	5
Yan, 2012	China	36	39	52.5±5.63	51.3±6.17	Manual acupuncture	Vitamin B1+Vitamin B12	75	75	2
Xu, 2010	China	32	32	38-77	38-77	Manual acupuncture	Mecobalamine	64	64	2
Liu, 2009	China	30	30	64.8	62.6	Manual acupuncture	Vitamin B1+Vitamin B6	60	60	4

Abbreviations: T, treatment group; C, control group.

Figure 3. Total effective rate subgroup analysis forest plots.

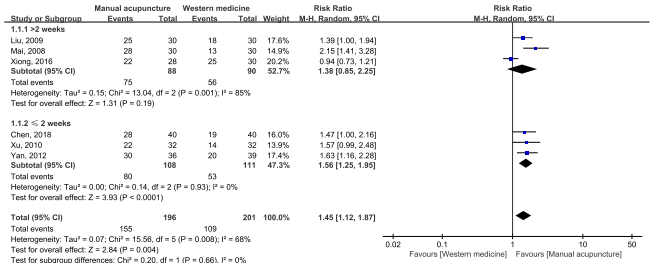
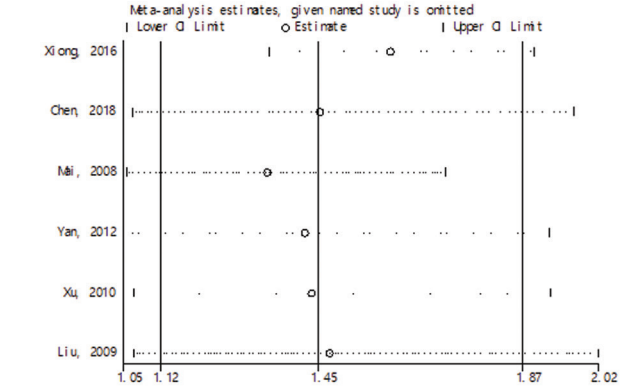


Figure 4. Sensitivity analysis for total effective rate.



According to the numeric rating scale score analysis, there was a statistically significant difference ($P < .05$) between manual acupuncture and Western medicine. However, there was no significant difference ($P > .05$) between electroacupuncture and Western medicine.

In terms of the visual analogue scale score, the analysis showed a significant difference ($P < .05$) between electroacupuncture and Western medicine. According to the descriptive analysis, there was a statistically significant difference ($P < .05$) in the peroneal nerve and ulnar nerve motor nerve conduction velocity when comparing acupuncture with Western medicine, acupuncture with acupoint injection and acupoint injection with Western medicine. In terms of sensory nerve conduction velocity of the peroneal or ulnar nerve, a descriptive analysis indicated a statistically significant difference ($P < .05$) between acupuncture and Western medicine, acupuncture and acupoint injection and acupoint injection and Western medicine.

When comparing manual acupuncture with Western medicine, there was a significant difference in sural nerve amplitude ($P < .05$). However, there was no significant difference between electroacupuncture and Western medicine ($P > .05$), according to the results of a descriptive analysis.

After performing the descriptive analysis, we found that there was no significant difference ($P > .05$) in the median nerve amplitude or sensory nerve conduction velocity of the median nerve between electroacupuncture and Western medicine.

Analysis of the sensory nerve conduction velocity of the sural nerve revealed that there was no significant difference between manual acupuncture and Western medicine, or between electroacupuncture and Western medicine in descriptive analysis ($P > .05$). Based on the descriptive analysis, there was no significant difference in peroneal nerve amplitude between manual acupuncture and Western medicine ($P > .05$).

Analysis of peroneal nerve motor nerve conduction velocity showed that there was no significant difference between manual acupuncture and Western medicine ($P > .05$).

A descriptive analysis found that there was no significant difference ($P > .05$) between tibial nerve amplitude in patients who received manual acupuncture vs patients who received Western medicine.A descriptive analysis comparing manual acupuncture to Western medicine regarding tibial nerve motor nerve conduction velocity revealed no significant difference ($P > .05$).

Subgroup Analysis

A study on manual acupuncture compared with Western medicine for CIPN made a subgroup analysis of the total effective rate based on the duration of treatment (>2 weeks vs ≤2 weeks). The findings revealed that manual acupuncture had a higher total effective rate than Western medicine in both groups ($P < .05$). The results of the subgroup analysis are shown in Figure 3.

Sensitivity Analysis

A sensitivity analysis of the results of the meta-analysis of the total effective rate of manual acupuncture compared with Western medicine for CIPN was performed. A case-by-case exclusion method was used, and the results indicated that the meta-analysis findings are reliable and consistent (see Figure 4).

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Figure 5. Evidence network diagram.

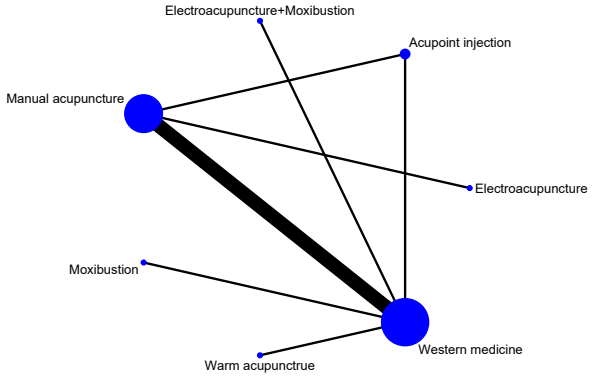
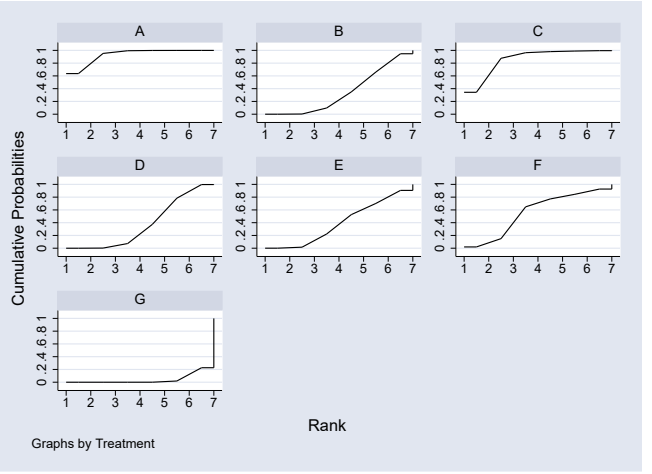


Figure 6. Network Meta-analysis of total effective rate.

A						
1.40 (0.26,7.56)	C					
3.49 (0.76,16.07)	2.50 (0.52,11.99)	F				
4.83 (1.32,17.66)	3.46 (0.90,13.26)	1.38 (0.45,4.30)	E			
5.05 (1.61,15.90)	**3.62 (1.05,12.54)**	1.45 (0.53,3.98)	1.05 (0.57,1.92)	D		
5.18 (1.55,17.30)	**3.71 (1.04,13.31)**	1.49 (0.52,4.25)	1.07 (0.55,2.10)	1.03 (0.71,1.49)	B	
6.98 (2.17,22.46)	**5.00 (1.48,16.95)**	2.00 (0.75,5.35)	1.44 (0.82,2.53)	**1.38 (1.10,1.74)**	1.35 (0.93,1.95)	G

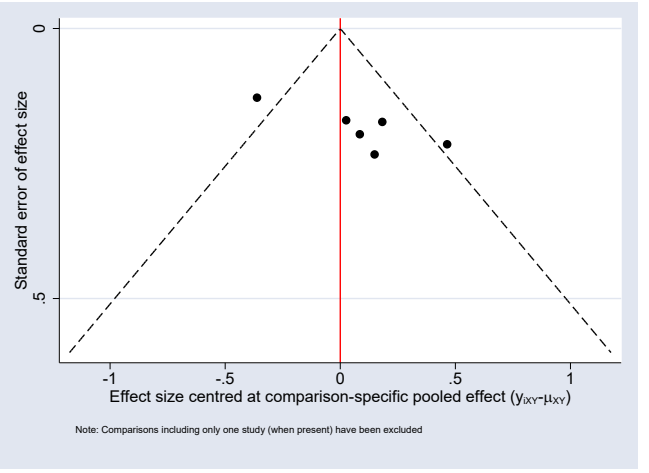
Note: A = electroacupuncture, B = acupoint injection, C = electroacupuncture + moxibustion, D = manual acupuncture, E = moxibustion, F = warm acupuncture, G = Western medicine.

Figure 7. The surface under the cumulative ranking curve plots.



Note: A=electroacupuncture, B=acupoint injection, C=electroacupuncture + moxibustion, D=manual acupuncture, E=moxibustion, F=warm acupuncture, G=Western medicine.

Figure 8. Publication bias.



Comparison Results of Network Meta-analysis

Evidence network diagram

Figure 5 displays the evidence network diagram, which illustrates a closed loop of manual acupuncture, acupoint injection and Western medicine. In order to assess any inconsistencies, this NMA utilized the node-splitting method. The node-splitting method revealed that there was no statistically significant difference ($P = .259$, $P > .05$) between the results of direct and indirect comparisons, indicating that there is no inconsistency between the two.

Results of network meta-analysis

According to the NMA results, electroacupuncture was more effective than moxibustion, manual acupuncture, acupoint injection and Western medicine in improving the total effective rate of CIPN. In addition, the combination of electroacupuncture + moxibustion was more effective than manual acupuncture alone. Furthermore, manual acupuncture was found to be more effective than Western acupuncture. The results of the NMA are presented in Figure 6.

Rank probabilities

Based on the SUCRA ranking, electroacupuncture showed the highest effectiveness (93.1%) in treating CIPN compared with other methods such as electroacupuncture + moxibustion (85.6%), warm acupuncture-moxibustion (55.1%), moxibustion (39.6%), manual acupuncture (37.5%), acupoint injection (35%) and Western medicine (4.1%) (see Figure 7).

Small sample effect estimation

Comparison-corrected funnel plots were drawn to check for any small sample effect in the intervention network. The findings suggest that there could be small sample effects or publication bias, as shown in Figure 8.

DISCUSSION

In our study, 13 RCTS involving 746 patients were analyzed. Our main objective was to assess the effectiveness of 6 acupuncture therapies for CIPN. Our study findings revealed that electroacupuncture had a higher success rate than other therapies, such as moxibustion, manual acupuncture, acupoint injection and Western medicine. In addition, the combination of electroacupuncture and moxibustion was found to be more effective than manual acupuncture, acupoint injection and Western medicine. The SUCRA ranking indicated that electroacupuncture was the most successful treatment for improving the clinical efficacy of Chemotherapy-induced peripheral neuropathy (CIPN).

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During chemotherapy, approximately 30% to 40% of patients experience CIPN, a toxic adverse event.[37] Although the pathogenesis of CIPN has not yet been fully elucidated, it is believed that the development of CIPN is associated with intraepidermal nerve fiber damage, oxidative stress, altered neuronal ion channel gene expression, upregulation of pro-inflammatory cytokines and activation of the neuroimmune system.[38-42] Studies now show that acupuncture can attenuate CIPN by modulating the 5-hydroxytryptamine system in the dorsal root ganglia, the dorsal horn of the spinal cord and duodenum, reducing oxidative stress and neuroinflammation.[43-45] Results of multiple RCTs[24,25,27,30,33,36] showed that acupuncture improves the efficacy of CIPN treatment. A meta-analysis conducted by Jin, et al[46] found that acupuncture significantly improved the overall effectiveness of CIPN treatment and additional meta-analyses have produced similar findings.[18-20] However, these meta-analyses did not compare the individual efficacy of different acupuncture therapies but rather different therapy combinations. As a result, the findings could have been more conclusive. In contrast, our NMA conducted both direct and network comparisons of various acupuncture therapies, which provided stronger support for the previous research. The study also found that electroacupuncture was the most effective, offering an alternative treatment option for CIPN. Furthermore, subgroup analysis demonstrated that manual acupuncture had a better total effectiveness rate than the Western medicine group for intervention times of both more than or less than 2 weeks. Moreover, it has been shown that acupuncture can effectively relieve CIPN symptoms in a short amount of time. Not only does this treatment method alleviate the economic burden, but it also improves patient QoL. These benefits are evident from the perspectives of healthcare providers, society and patients.

CIPN is a type of nerve damage in the peripheral nervous system due to chemotherapy drugs.[47,48] This damage to sensory nerves can lead to symptoms such as numbness, pain, pins and needles and a burning sensation in the hands and feet.[49] Damage to motor nerves can result in a loss of deep tendon reflexes, muscle weakness and balance difficulties.[50] Our meta-analysis attempted to evaluate nerve conduction velocity because it is the gold standard for diagnosis of peripheral neuropathy.[51] Due to the small amount of available literature on different nerve conduction velocities in this study, only a descriptive analysis was performed. Most acupuncture therapies yielded positive results in the following aspects: peroneal nerve motor nerve conduction velocity, ulnar nerve motor nerve conduction velocity, peroneal nerve sensory nerve conduction velocity, ulnar nerve sensory nerve conduction velocity and other outcome indicators. A meta-analysis by Jin, et al[46] revealed that acupuncture has the ability to restore nerve conduction velocity. Friedemann, et al.[52]showed that acupuncture can enhance structural regeneration in CIPN as measured by nerve conduction studies in subjective improvement and neurological findings. Acupuncture also enhances the speed of sensory and motor nerve conduction in the extremities while providing nerve protection. Moreover, acupuncture has been observed to have analgesic effects through gating mechanisms in the human spinal cord,[53,54] and may also reduce pain symptoms by inhibiting cyclooxygenase-2 and releasing endogenous opioid peptides.[55,56] Electroacupuncture stimulation reduces paclitaxel-induced neuropathic pain mediated by spinal opioid receptors, α2 and β-adrenergic receptors.[57] According to the descriptive analysis of this study, acupuncture was found to improve pain symptoms in CIPN, which is consistent with the results of the meta-analysis by Jin, et al.[46] In addition, guidelines recommend acupuncture as a complementary alternative therapy for peripheral neuropathy.[17]

Based on the NMA findings, electroacupuncture is the most effective treatment of the 6 acupuncture therapies studied for improving CIPN. Like other acupuncture therapies, electroacupuncture can help regulate nerve function and alleviate pain symptoms by stimulating specific acupuncture points. However, what sets electroacupuncture apart is its unique therapeutic approach that combines electrical stimulation with needling. This approach can have a profound impact on nerve conduction and regulation, resulting in a better therapeutic outcome. By using pulsed electric current, electroacupuncture can trigger the release of pain-related endogenous opioid receptors, which can help alleviate pain and numbness symptoms.[58] This approach allows for precise control of the intensity and frequency of stimulation, which can be tailored to each patient's needs for more personalized treatment.[59] Compared with regular acupuncture therapy, it involves a longer stimulation time and may result in a longer-lasting effect. In addition, electroacupuncture has been found to inhibit the secretion of pro-inflammatory cytokines, increase local neurotrophic nutrition, improve microcirculation and promote nerve cell regeneration, all of which can help prevent neurotoxicity.[57,60,61] Electroacupuncture can enhance patients' QoL by reducing their pain level, increasing nerve conduction velocity in their limbs and improving limb functionality. It's important to note that while electroacupuncture is the most effective treatment for CIPN according to the results of this NMA, the specific treatment regimen should be tailored to each patient's unique situation and the physician's clinical experience. The frequency selection of electroacupuncture for CIPN requires further exploration. In addition, selecting appropriate acupoints is crucial to achieving the desired therapeutic effect and is one of the critical issues that need to be addressed.

This study has several strengths. First, it is the first study to use NMA to compare the effectiveness of 6 different acupuncture therapies. We found that electroacupuncture is the best therapy for improving CIPN. Second, a subgroup analysis was conducted since CIPN requires a relatively long treatment duration. The total effective rate of acupuncture was found to be superior to that of the Western medicine group for both intervention durations of >2 weeks and ≤2 weeks. Therefore, our study suggests that acupuncture can effectively treat CIPN in a short period. In the future,

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comparisons of acupuncture therapies with different durations within 2 weeks could be conducted. Third, this NMA has been registered on PROSPERO and follows PRISMA-NMA guidelines to reduce bias.

Study Limitations

There are several issues with this particular NMA that need to be addressed. First, the majority of the RCTs did not mention allocation concealment and blinding, which could have a negative impact on the validity of the study results. Second, the small sample size of the research trials included in the analysis could potentially affect the accuracy of the findings. In addition, as the literature included in the analysis was limited, it was not possible to perform subgroup analyses on other factors that could have had an impact on the efficacy of the treatment, which may have led to some study bias. Third, this study conducted a meta-analysis of the total effective rate. However, due to the limited number of RCTs, only a descriptive analysis was performed for pain score, nerve conduction velocity and nerve conduction wave amplitude. Therefore, it was not feasible to compare the effects of acupuncture treatments on these factors through networking. Thus, the findings require further validation in future studies. Fourth, there was some publication bias and a small sample effect in this NMA, which may have affected the reliability of the conclusions.

CONCLUSION

To sum up, by comparing the total effective rate of 6 different acupuncture therapies in this NMA, we found that electroacupuncture is the most effective therapy for improving CIPN. However, more multi-center and larger sample RCTs are required to confirm these findings as the number of included RCTs was limited.

STATEMENT OF ETHICS

The authors have no ethical conflicts to declare. This systematic review and meta-analysis was conducted according to the PRISMA-NMA statement guidelines. An ethics statement is not applicable because this study is based exclusively on published literature.

CONFLICT OF INTEREST STATEMENT

None.

FUNDING SOURCES

None.

AUTHOR CONTRIBUTIONS

Teng Zhang and Qiang Zhang have contributed equally to this work and are co-first author

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Table S1. PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-Analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	***2***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (eg, Web address); and, if available, provide registration information, including registration number.	None
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***3***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	3
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***none***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3-4
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	4
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	4
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	**4**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***4***
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	40
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***4***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***4***
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (1) simple summary data for each intervention group, and (2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***4***

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Table S1. (continued)

Section/Topic	Item #	Checklist Item	Reported on Page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (eg, placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***4-7***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***none***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	4
Results of additional analyses	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***4-7***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users and policy-makers).	7-8
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (eg, avoidance of certain comparisons).*	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***9***

Table S2. Pubmed Search Strategy

Number	Search terms
#1	Peripheral Nervous System Diseases[MeSH]
#2	Peripheral Nerve Diseases[Title/Abstract]
#3	Peripheral Neuropathies[Title/Abstract]
#4	PNS (Peripheral Nervous System) Diseases[Title/Abstract]
#5	PNS Diseases[Title/Abstract]
#6	Peripheral Nervous System Disease[Title/Abstract]
#7	Peripheral Nervous System Disorders[Title/Abstract]
#8	Nerve Disease, Peripheral[Title/Abstract]
#9	Nerve Diseases, Peripheral[Title/Abstract]
#10	Neuropathy, Peripheral[Title/Abstract]
#11	PNS Disease[Title/Abstract]
#12	Peripheral Nerve Disease[Title/Abstract]
#13	Peripheral Neuropathy[Title/Abstract]
#14	OR/1-13
#15	Neoplasms[MeSH]
#16	Cancer[Title/Abstract]
#17	Tumors[Title/Abstract]
#18	Benign Neoplasms[Title/Abstract]
#19	Neoplasia[Title/Abstract]
#20	Neoplasm[Title/Abstract]
#21	Neoplasms, Benign[Title/Abstract]
#22	Benign Neoplasm[Title/Abstract]

Number	Search terms
#23	Cancers[Title/Abstract]
#24	Neoplasm, Benign[Title/Abstract]
#25	Tumor[Title/Abstract]
#26	OR/15-25
#27	Acupuncture [MeSH]
#28	Electroacupuncture[MeSH]
#29	Acupuncture Therapy[MeSH]
#30	Acupuncture Treatments [Title/Abstract]
#31	Acupuncture Treatment [Title/Abstract]
#32	Treatment, Acupuncture [Title/Abstract]
#33	Therapy, Acupuncture [Title/Abstract]
#34	Acupuncture [Title/Abstract]
#35	Pharmacopuncture [Title/Abstract]
#36	Electroacupuncture [Title/Abstract]
#37	Warm needle [Title/Abstract]
#38	Fire needle [Title/Abstract]
#39	Blood-letting therapy [Title/Abstract]
#40	Warm acupuncture [Title/Abstract]
#41	Fire acupuncture [Title/Abstract]
#42	Moxibustion [MeSH]
#43	Moxibustion [Title/Abstract]
#44	Auricular application pressure [Title/Abstract]

Number	Search terms
#45	Auricular needle [Title/Abstract]
#46	Acupoint catgut embedding [Title/Abstract]
#47	Acupoint injection [Title/Abstract]
#48	Abdominal needle [Title/Abstract]
#49	Ear acupuncture [Title/Abstract]
#50	Ear needle [Title/Abstract]
#51	Auricular needle [Title/Abstract]
#52	Auricular acupuncture [Title/Abstract]
#53	Acupoint [Title/Abstract]
#54	Acupressure [Title/Abstract]
#55	Auricular pressure [Title/Abstract]
#56	OR/27-55
#57	Randomized Controlled Trials as Topic[MeSH]
#58	Clinical Trials, Randomized[Title/Abstract]
#59	Controlled Clinical Trials, Randomized[Title/Abstract]
#60	Trials, Randomized Clinical[Title/Abstract]
#61	Random*[Title/Abstract]
#62	Randomized Controlled Trial[Title/Abstract]
#63	Randomized Controlled Trials[Title/Abstract]
#64	OR/57-63
#65	#14 AND #26 AND #56 AND #64

Table S3. Descriptive Analysis Results

Outcome index	Comparison category	Number of studies	Descriptive analysis results		
			RR (95% CI)	SMD (95% CI)	*P* value
Total effective rate	Acupoint injection vs Western medicine	1	1.12(0.93, 1.35)	NA	.248
	Electroacupuncture+Moxibustion vs Western medicine	1	**5.00(1.61, 5.50)**	NA	**.005**
	Manual acupuncture vs Acupoint injection	1	0.84(0.68, 1.05)	NA	.126
	Manual acupuncture vs Electroacupuncture	1	**0.20(0.07, 0.57)**	NA	**.003**
	Moxibustion vs Western medicine	1	**1.44(1.04, 2.00)**	NA	**.026**
	Warm acupuncture vs Western medicine	1	2.00(0.84, 4.78)	NA	.119
NRS	Electroacupuncture vs Western medicine	1	NA	0.17(-0.56, 0.90)	.645
	Manual acupuncture vs Western medicine	1	NA	**-1.40(-2.12, -.69)**	**<.0001**
VAS	Electroacupuncture vs Western medicine	1	NA	**-1.15(-2.11, -0.20)**	**.018**
Peroneal nerve MCV	Acupuncture vs Western medicine	1	NA	**-0.77(-1.31, -0.24)**	**.005**
	Acupuncture vs Acupoint injection	1	NA	**-2.04(-2.69, -1.40)**	**<.0001**
	Acupoint injection vs Western medicine	1	NA	**1.64(1.04, 2.23)**	**<.0001**
Ulnar nerve MCV	Acupuncture vs Western medicine	1	NA	**-2.69(-3.41, -1.97)**	**<.0001**
	Acupuncture vs Acupoint injection	1	NA	**-4.74(-5.77, -3.72)**	**<.0001**
	Acupoint injection vs Western medicine	1	NA	**1.87(1.25, 2.48)**	**<.0001**
Peroneal nerve SCV	Acupuncture vs Western medicine	1	NA	**-1.89(-2.51, -1.27)**	**<.0001**
	Acupuncture vs Acupoint injection	1	NA	**-3.11(-3.89, -2.33)**	**<.0001**
	Acupoint injection vs Western medicine	1	NA	**1.65(1.06, 2.25)**	**<.0001**
Ulnar nerve SCV	Acupuncture vs Western medicine	1	NA	**-1.59(-2.18, -1.00)**	**<.0001**
	Acupuncture vs Acupoint injection	1	NA	**-3.43(-4.26, -2.61)**	**<.0001**
	Acupoint injection vs Western medicine	1	NA	**1.79(1.19, 2.40)**	**<.0001**
Sural nerve amplitude	Electroacupuncture vs Western medicine	1	NA	0.46(-0.28, 1.20)	.221
	Manual acupuncture vs Western medicine	1	NA	**0.85(0.19, 1.52)**	**.012**
Median nerve amplitude	Electroacupuncture vs Western medicine	1	NA	0.22(-0.51, 0.95)	.548
Median nerve SCV	Electroacupuncture vs Western medicine	1	NA	-0.74(-1.49, 0.01)	.055
Sural nerve SCV	Manual acupuncture vs Western medicine	1	NA	0.26(-0.38, 0.90)	.419
	Electroacupuncture vs Western medicine	1	NA	0.27(-0.47, 1.00)	.475
Peroneal nerve amplitude	Manual acupuncture vs Western medicine	1	NA	0.26(-0.38,0.89)	.434
Peroneal nerve MCV	Manual acupuncture vs Western medicine	1	NA	0.16(-0.48, 0.79)	.631
Tibial nerve amplitude	Manual acupuncture vs Western medicine	1	NA	0.35(-0.29, 0.99)	.281
Tibial nerve MCV	Manual acupuncture vs Western medicine	1	NA	0.20(-0.43, 0.84)	.530

Abbreviations: CI = confidence interval; MCV = motor nerve conduction velocity; NA = data unavailable; NRS = numeric rating scale; RR = relative risk; SCV = sensory nerve conduction velocity; SMD = standard mean difference; VAS = visual analogue scale.