

# A systematic review and meta-analysis of the efficacy of acupuncture and electroacupuncture against chemotherapy-induced peripheral neuropathy

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#### Abstract

**Background:** Chemotherapy-induced peripheral neuropathy (CIPN) occurs in 68.1% of patients within the first month of undergoing chemotherapy; however, standardized treatment for CIPN has not been established yet. The efficacy of acupuncture, a widely used treatment for CIPN in South Korea, has not been studied sufficiently. This study aimed to review the studies that evaluated the efficacy of acupuncture or electroacupuncture (EA) in treating CIPN.

**Methods:** A literature search was performed on relevant international databases — MEDLINE, Embase, the Allied and Complementary Medicine Databases, and China National Knowledge Infrastructure — as well as Korean databases — the National Digital Science Library, Oriental Medicine Advanced Searching Integrated System, DBpia, and Korean Studies Information Service System. Randomized controlled trials (RCTs) that aimed to treat CIPN symptoms with acupuncture or EA and set not only a control group with a conventional pharmacological treatment or injection, but also a placebo control or sham-acupuncture group, were included. Meta-analysis was conducted to elucidate the efficacy of acupuncture/EA on the basis of symptom score.

**Results:** Of the 13 studies included in the literature review, 12 RCTs compared acupuncture and pharmacological treatments. There were 3 EA RCTs, but only 1 RCT compared EA and sham-EA. A total of 832 participants were included in these studies. Five RCTs showed that acupuncture was more effective than pharmacological treatment in terms of efficacy rate. Regarding the risk of bias summary, the quality of included studies was poor. Only 1 study compared the efficacy of EA and sham EA; therefore, the specific efficacy of acupuncture could not be elucidated.

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M-SH and H-YL contributed equally to this work.

JHL and TYP contributed equally to the study.

Ethical approval and patient consent were not necessary, because the systematic review was based on previously published research.

The study findings will be disseminated in peer-reviewed journals and presented at national and international conferences. The data from this work will be made available upon request.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Conclusion:** Acupuncture is safe, but the symptom-alleviating effect on CIPN can hardly be determined because of methodological deficiencies of the included studies. In terms of the clinical efficacy rate, acupuncture was more effective than conventional pharmacological treatments.

#### PROSPERO registration number: CRD42018111509.

**Abbreviations:** AE = adverse events, CIPN = chemotherapy-induced peripheral neuropathy, EA = electroacupuncture, NCV = nerve conduction velocity, NRS = numerical rating scale, RCT = randomized controlled trials, ROB = risk of bias, VAS = visual analog scale.

Keywords: acupuncture, chemotherapy-induced peripheral neuropathy, electroacupuncture, systematic review

# 1. Introduction

Cancer is the leading cause of death worldwide, accounting for 8.2 million deaths in 2012. The annual number of cancer cases worldwide is expected to increase from 14 million in 2012 to 22 million over the next 20 years.<sup>[1]</sup> Chemotherapy is a type of cancer treatment in which cytotoxic chemicals are administered intravenously to remove tumors or reduce their size.<sup>[2]</sup> In most cases, chemotherapy has considerable side effects. Chemotherapy drugs are known to be neurotoxic and damage peripheral nerves, ultimately leading to chemotherapy-induced peripheral neuropathy (CIPN).<sup>[3]</sup> The main symptoms of CIPN are nerve pain in the upper and lower extremities, sensory nerve loss, and motor nerve loss. CIPN is one of the common side effects in patients receiving chemotherapy. According to a systematic review, the prevalence rate of CIPN is 68.1% in the first month of chemotherapy.<sup>[4]</sup>

More importantly, CIPN may limit the effectiveness and prolong the duration of chemotherapy, because — as a general management strategy for CIPN — it may be necessary to reduce the dose of anticancer drugs or to temporarily stop treatment if symptoms become severe.<sup>[5,6]</sup> Drugs acting on the central nervous system such as pregabalin and gabapentin may be used to temporarily relieve the symptoms,<sup>[7]</sup> but evidence regarding their efficacy against CIPN remains unclear.<sup>[8]</sup> Acupuncture, the main form of treatment in traditional Korean medicine, has been used as an adjuvant therapy to relieve symptoms of CIPN. Previous studies have reported that acupuncture is clinically effective for CIPN<sup>[9,10]</sup> and that it improves nerve conduction velocity (NCV) with its effects lasting for 1 month.<sup>[10,11]</sup>

Electroacupuncture (EA), which involves electrical stimulation of acupuncture needles, was introduced relatively later than acupuncture itself, but its use is increasing.<sup>[12,13]</sup> Nevertheless, the effect of EA on CIPN is controversial.<sup>[14]</sup>

Therefore, our research team planned a practical clinical trial to investigate the effectiveness of traditional Korean medicine techniques such as acupuncture and EA on CIPN. Before the clinical study, we systematically reviewed the published clinical studies on the treatment of CIPN using acupuncture and EA to evaluate their effects.

## 2. Methods

### 2.1. Study protocol and registration

The study protocol was published in the journal *Medicine* in March 2019,<sup>[15]</sup> and the study was registered in PROSPERO (registration number: CRD42018111509).

#### 2.2. Inclusion criteria

All randomized controlled trials (RCTs) that used acupuncture to manage CIPNs were included in the review with no restriction on publication status and no limitation on acupuncture techniques and cancer type, age, sex, or race of patients diagnosed with CIPNs. However, such RCTs were included only if they used a placebo or sham-treatment group as a control group and a conventional pharmacological treatment group or an injection treatment group as an active treatment group. Furthermore, primary outcomes such as visual analog scale (VAS) or numerical rating scale (NRS) scores for CIPN and secondary outcomes including

(1) efficacy rate (number of patients with improved symptoms),

- (2) NCV, and
- (3) adverse events (AEs) were criteria for inclusion in this study.

#### 2.3. Search methods for the identification of studies

We searched for articles related to acupuncture, EA, and CIPN published domestically and internationally until September 2018. Online searches were performed in international databases such as MEDLINE, Embase, the Allied and Complementary Medicine Databases, and China National Knowledge Infrastructure, as well as Korean databases, namely the National Digital Science Library, Oriental Medicine Advanced Searching Integrated System, DBpia, and Korean studies Information Service System. The detailed search strategy used in the PubMed database is presented in Appendix A, http://links.lww.com/MD/E62, http://links.lww.com/MD/C912.<sup>[15]</sup> The search terms were translated into an appropriate language and used according to the database (the search strategy used in China National Knowledge Infrastructure is presented in Appendix B, http://links.lww.com/MD/E63).

**2.3.1.** Searching other resources. A reference list of previously published review articles was retrieved to search for literature not found in the online databases. Abstracts presented at relevant conferences were manually retrieved.

#### 2.4. Data collection and analysis

**2.4.1. Selection of studies.** Two researchers (MSH, TYC) independently conducted literature searches and excluded noticeably inapplicable studies on the basis of titles and abstracts. The text of each study was then reviewed to determine whether each study was suitable for our analysis. Related work was done using EndNote and Excel programs. A detailed reason was recorded for excluding studies, and the differences were resolved through discussion between the 2 researchers. If no consensus



Figure 1. PRISMA flow chart of systematic review selection. AMED = allied and complementary medicine databases, AT = acupuncture, CIPN = chemotherapy induced peripheral neuropathy, CNKI = China National Knowledge Infrastructure, KISS = Korean Studies Information Service System, RCT = randomized controlled trial, RISS = research information service system, UOS = uncontrolled observational study.

was reached, an independent reviewer was consulted. Details regarding the selection of included studies are summarized in the PRISMA flowchart (Fig. 1).

**2.4.2. Data extraction and management.** Two researchers (MSH, HYL) reviewed the text of each study and extracted data on study design, blinding, intervention, controls, results, key findings, and other details that were to be analyzed and tabulated.

**2.4.3.** Assessment of risk of bias (ROB). The ROB was independently evaluated by 2 authors (MSH, HYL) using the Cochran " ROB" assessment, which includes randomization of sequence generation, assignment concealment, blinding of participants and outcome assessors, incomplete outcome data, and other biases. The ROB was classified as high, unclear, and low.<sup>[16]</sup>

**2.4.4.** Measures of treatment effect. To summarize the effects of acupuncture and EA on CIPN in each study, relative risks for dichotomous variables and standardized mean differences and 95% confidence intervals for continuous variables were

presented. If heterogeneity was identified among the populations and interventions among the studies, the results of the included studies were synthesized using a random-effects model.

**2.4.5. Dealing with missing data.** In case of missing or insufficient data, the author of the corresponding article was contacted by e-mail or telephone to obtain necessary information. If we could not recover sufficient data, the article was discarded. The analysis was based on the available data, and the potential impact of missing data is discussed herein.

**2.4.6.** Assessment of heterogeneity. Heterogeneity of the results was analyzed using the  $\chi^2$  test and determined using the  $I^2$  value. It was determined that statistical heterogeneity between tests could be neglected if  $I^2$  was less than 50%, and the effect size was estimated using a fixed-effect model. If  $I^2$  exceeds 50%, there is considerable heterogeneity between trials; therefore, a subgroup analysis was performed to determine possible reasons.

2.4.7. Assessment of reporting bias. The assessment of reporting bias using funnel plots and *P*-values, as described by

Summary of	the included studies.					
Study ID	Disease (condition)	Intervention (experimental)	Control	Outcome	AT point	AT details
Chen 2018	Oxaliplatin-induced peripheral neurotoxicity with colorectal cancer	(A) AT (n=40)	(B) Medication (intramuscular injection of mecobalamin 0.5 mg, weekly treatment 3 times, total 2 wk. n = 40)	1. Efficacy rate	ST36, CV6, SP3, LI4, LI11, LR3, EX-UE9, EX-LE10 EX-UE11, ST40, SP10, SP6, Kl3	30 min, weekly 5 times; 2 wk
Tian 2016	CIPN caused by FOL-FOX4 regimen	(A) AT (n=30)	(B) Medication in exp (B) Medication (injected cobamamide 1 mg, once a day, 14-d course, n = 30)	1. Efficacy rate 2. NCV, SCV, MCV 3. QOL	LITO, LJ4, LITT, TE5, EX-UE9, GB34, ST36, ST40, SP6, GB40, LR3, EX-LETO, CV4, CV6, GV20	30 min, twist the needle once, 14-d course
Wu 2014	Oxaliplatin-induced peripheral neurotoxicity	(A) AT (n=20)	(B) Medication (intravenous mecobalamin qd while giving chemotherapy, continuous 6 d, n = 19) (C) No treatment (Chenotherapy alone. n = 19)	<ol> <li>Incidence of neurotoxicity</li> <li>Efficacy rate</li> </ol>	LI11, PC6, LI4, SP10, ST36, SP6, Upper: EX-UE11, EX- LE12 (bloodletting) Motor dysfunction or muscular atrophy: GB34, ST40	Once a day, 6 d
Sun 2012	Oxaliplatin-induced peripheral neurotoxicity	(A) EA plus (B) (n=34)	(B) Medication (glutathione, daily for 14 d, $n = 32$ )	1. Efficacy rate 2. NCV, SCV, MCV	ST36, CV4, SP10 According to Zheng (certificate): LI4, L111, TE10, TE4, L5, SI4, EX-UE9, SI3, ST35, ST34, SP6, SP9, ST41, KI3, BL60, BL62, KI6, EX-LE10, LR3 EX-LE10, LR3	30 min, once a day; 14 d,
Hau 2011	CIPN with malignant tumor	(A) AT (n=20)	(B) Medication (Metoclopramide injection intramuscularly, 10 mg each time, once or twice a day, granisetron oral, 1 mg each time, once dally, peripheral nerve toxicity above degree II for adenosylcobalamin injection, n = 20)	<ol> <li>Incidence of neurotoxicity</li> <li>The incidence and score of digestive tract adverse effects</li> </ol>	LI11, PC6, LI4, ST 36, SP6, GB34	30 min, once a day; 2 wk
Wang 2011	Oxaliplatin-induced peripheral neurotoxicity with colorectal cancer	(A) AT (n=30)	<ul> <li>(B) Medication (intramuscular injection of Cobamamide, n= 30)</li> </ul>	1. Efficacy rate	Ll4, Ll10, Ll11, ST36, ST32, GB30, ST40, GB34, GB31, EX-LE10 Early patient: BL20, LR3 Late patient: SP6, K13, SP10, Finger or tiptoe numbness: EX-LE12, EX-UE11 (bloodletting)	30 min, once a day; 14-d course
Xu 2010	Pacifitaxel or oxaliplatin-induced peripheral neurotoxicity	(A) AT (n=32)	<ul> <li>(B) Medication (intramuscular injection of cobamamide, n= 32)</li> </ul>	1. Efficacy rate	LI4, LR3, ST36, CV6, LI11, SP3, EX-UE9, EX-LE 10 Early patient: SP10 Late patient: SP6, Kl3 Upper: EX-UE11, EX-LE12 (bloodletting) Motor dysfunction or muscular atrophy: GB34, ST40	30 min, once a day; 14-d course
						(continued)

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Table 1

Study ID Disease (cor Liu 2009 CIPN with malignant						
Liu 2009 CIPN with malignant	ndition)	Intervention (experimental)	Control	Outcome	AT point	AT details
	it tumor	(A) AT (n=30)	(B) Medication (intramuscular injection of B vitamins, once a day, 14 d is a course of treatment, the first 3 d of chemotherapy began, total 2 courses of treatment, $n = 30$ )	1. Efficacy rate	ST36, SP6, GB34, LI4, LI11, K116, CV4, CV6 Upper extremity paralysis: HT3, L110, LU7, LU11, TE5, PC4, TE3, SP12, EX-UE9 Lower extremity paralysis: GB30, GB31, BL40, ST40, SP6, GB38, GB40, LR4, BL60, EX-LE10	30 min, once a day; 14-d course, total 2 courses
Mai 2008 CIPN with malignan	it tumor	(A) AT (n=30)	(B) Medication (intramuscular injection of B vitamins, once a day, 10 d is a course of treatment, the interval of treatment was 3 d, total 3 courses of treatment, n = 30)	1. Efficacy rate	GB20, TE5, ST36, BL40, GB34, ST40, SP6, LR3, SP10	Once a day, 10-d course, 3-d interval, 3 courses
Li 2012 CIPN with malignan	it tumor	(A) EA plus (B) $(n = 40)$	<ul> <li>(B) Herbal medicine (Jianpi Bushen Jiedu decoction, n= 40)</li> </ul>	<ol> <li>Incidence of neurotoxicity</li> <li>Kamofsky score</li> <li>QOL</li> </ol>	ST36, SP6, LI11, GV20, CV4, CV6	14-d course
Han 2017 CIPN with multiple I	myeloma	(A) AT plus (B) (n=49)	<ul> <li>(B) Met methylcobalamin (500 μg</li> <li>IM every other day for 20 d;</li> <li>+ 500 μg PO, 3 times per day for 2 mo) (n = 49)</li> </ul>	<ol> <li>VAS pain score</li> <li>FACT/G0G-NTX questionnaires</li> <li>NCV (median n., peroneal n.)</li> </ol>	Bilaterally LR3, ST43, GB41, SP6, ST36, SP10, ST25, GV14, GV12, GV11 GV9. BL13, BL17, BL58	Once a day for 3 d, then once every alternate day for 10 d as a treatment cycle; 3 cycles
Greenlee 2016 Patients with stage cancer schedulec taxane therapy	I-III breast d to receive	(A) EA (n=25)	(B) Sham EA group (n=23)	1. BPI-SF 2. FACT/GOG-NTX 3. Others	<ol> <li>(1) General GB34, ST36, Ll4, Ll10</li> <li>(2) Lower limb - EX-B2 (L3, L5), EX-LE10</li> <li>(3) Upper limb - EX-B2 (C5, C7), EX-UE9</li> </ol>	2 Hz of mixed pulsatile intervals for a total of 30 min
Rostock 2013 Patients with cance.	r and CIPN	(A) EA (n=14)	<ul> <li>(B) Hydroelectric baths (n = 14)</li> <li>(C) High doses of vit B1, B6 (n = 15)</li> <li>(D) placebo (n = 17)</li> </ul>	<ol> <li>NRS</li> <li>Neuropathy score</li> <li>NCV (median n., sural n.)</li> <li>NCI-CTC</li> <li>EORTC-QLQ C30</li> </ol>	LV3, SP9, GB41, GB34, L/4, L111, SI3, HT3	$8 \pm 1$ sessions of EA for 3 wk

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AI = acupurcture, brt-sr = orter pair inventory-strort form, utriv = chemometapy induced perphetal neuropatry, the electroacupuncture, EUKIC-GLU = European Urganization for Research and Treatment of Cancer-Guality of Life Questionnaire, FACI/GUG-NIX =Tunctional assessment of cancer therapy/gynecologic oncology group-neurotoxicity, MCV = motor nerve conduction velocity, n, = nerve, NCI-CIC = National Cancer Institute-common toxicity criteria, NCV = nerve conduction velocity, MCV = motor nerve conduction velocity, n, = nerve, NCI-CIC = National Cancer Institute-common toxicity criteria, NCV = nerve conduction velocity, NRS = numeric rating scale, QOL = quality of life, SCV = sensory nerve conduction velocity, VAS = visual analog scale, QOL = quality of life, SCV = sensory nerve conduction velocity, VAS = visual analog scale.

# Table 2

Grading of recomn	nendations asses	sment, developme	ent, and evaluatio	n (GRADE) sumn	nary.	
No. of nonlininous	Disk of hiss	Inconsistence	Indianaturan	Immunaciaian	Dublication bios	Ourseall musel

No. of participants	RISK OF DIAS	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
832 (13 RCTs)	Serious*	Not serious	Not serious	Serious <sup>†</sup>	None	⊕⊕ <sup>∞</sup> LOW

RCT = randomized controlled trial

\* Lack of blinding outcome assessors.

<sup>+</sup> Optimal information size is not met.

Egger et al, was not conducted because data from less than 10 studies were finally included in the meta-analysis.<sup>[17,18]</sup>

**2.4.8. Grading the quality of evidence.** Grading of recommendations, assessment, development, and evaluations was used to assess the quality of the evidence for the key findings. The quality of evidence was divided into 4 levels: high, medium, low, and very low.

## 3. Results

#### 3.1. Study selection

During the initial search, 190 articles were extracted, of which 39 were excluded as duplicates. As a result of title- and abstractbased screening, 118 articles were excluded. After a full-text review of the remaining 33 articles, 13 articles were finally selected (Fig. 1).

#### 3.2. Participants

A total of 832 participants were included in the 13 selected articles. All participants were diagnosed with CIPN (Table 1).

#### 3.3. Intervention

**3.3.1.** Acupuncture intervention. Ten studies<sup>[19–28]</sup> used manual acupuncture and 3 studies<sup>[14,29,30]</sup> used EA. In these 13 articles, the most frequently used acupuncture points were ST36 and SP6 (12 times) and LI4 and LI11 (9 times), followed by GB 34, ST40, LR3, EX-LE 10, CV6, EX-UE 9, LI10, SP10, KI3, CV 4, EX-UE 11, TE 5, GV20, EX-LE 12, and SI3 in descending order. The frequency of treatment ranged from twice a week to once a day, and the treatment period ranged from 6 to 21 days, with 14 days being the most common period of treatment (Table 1).

**3.3.2.** Control intervention. Nine of the 13 articles used vitamin B as a control intervention, and these studies administered it in the form of intramuscular injection with the exception of 1 study,<sup>[19]</sup> which administered it orally in the form of capsules. The remaining 4 studies used glutathione, metoclopramide, herbal medicine, or sham-EA. One study used hydroelectric bath, vitamin B, and placebo as control interventions (Table 1).

## 3.4. Outcomes

Among the 13 articles, 8 used clinical efficacy rate as outcome and 4 used NCV. VAS score was used to quantify pain in 1 document and NRS score to quantify symptoms in another (Table 1).

# 3.5. ROB

Although all the included articles have mentioned random sequence generation, only 6 of them have described it. One



Figure 2. Risk of bias summary: review authors' assessment of each risk of bias item for each included study.



Figure 3. Risk of bias graph: review authors' assessments of risk of bias items presented as percentages across all included studies.

study<sup>[14]</sup> generated random lists using the SAS program, and the remaining 5<sup>[19,21,24–26]</sup> used random numbers. Only 1 study<sup>[14]</sup> referred to allocation concealment using opaque envelopes. Only 1 study blinded the practitioner using sham-EA<sup>[30]</sup> possibly due to the difficulty of blinding considering the nature of acupuncture treatment. The grading of recommendations, assessment, development, and evaluations and assessment of ROB is summarized in Table 2 and Figures 2 and 3.

#### 3.6. Effect of interventions

One study compared EA with sham-EA,<sup>[30]</sup> and 3 studies compared acupuncture plus conventional treatments with conventional treatments alone.<sup>[20,23,29]</sup> Nine studies compared acupuncture and pharmacological treatments (Table 1).

**3.6.1. Efficacy rate.** Among the 13 studies involving 832 participants, 8 reported the number of patients with improved symptoms after treatment, but the standard for improved symptoms varied from study to study. In 3 studies,<sup>[19,23,27]</sup> peripheral neuropathy was graded (0–IV) according to the criteria described by Lévi et al<sup>[31]</sup>; these studies reported that the treatment was effective if there was a decrease in peripheral neuropathy grade (i.g. invalid = no change or increase in grade). In 3 other studies,<sup>[21,25,26]</sup> the patient's responses to a questionnaire on sensory and motor disorders was used to classify CIPN into 5 grades (0–4) according to Hausheer et al<sup>[32]</sup> (i.g. invalid = decrease or increase in rating).

In 1 study,<sup>[28]</sup> 0 to 6 points were assigned to abnormalities and pain in the limbs. The reduction in the total score was measured

and a reduction rate of 25% or more was considered valid (i.g. invalid = reduction rate <25%). One study<sup>[19]</sup> measured the rate of decrease in the total scores of symptoms including pain, fatigue, dizziness, breathing difficulty, spontaneous sweating, palpitation, and insomnia and regarded a reduction rate of more than 2/3 valid (i.g. invalid = reduction rate <1/3). Among the 8 studies that reported efficacy rates, meta-analysis included 5 studies with similar interventions and controls,<sup>[19,21,22,25–27]</sup> and the results are shown in Figures 4 and 5. Meta-analysis was performed for studies that used a similar method of deriving the efficacy rate, and the results showed that acupuncture was more effective than vitamin B injection treatment in terms of efficacy rate (Figs. 4 and 5).

**3.6.2. NCV.** Four studies used NCV as an outcome measure,<sup>[14,20,21,23]</sup> but meta-analysis could not be conducted because of difference in study design and control settings. The subjects of NCV analysis also differed from study to study, but all 4 studies measured NCV of medial nerve and sural nerve among sensory nerves. Sun et al<sup>[23]</sup> reported NCV results of medial nerve, ulnar nerve, tibial nerve, and peroneal nerve among motor nerves and medial nerve, ulnar nerve, and sural cutaneous nerve among sensory nerves. Tian<sup>[21]</sup> measured NCV of medial nerve and medial nerve among motor nerves and medial nerve among sensory nerves. Tian<sup>[21]</sup> measured NCV of medial nerve and common peroneal nerve among sensory nerves. Han et al<sup>[20]</sup> evaluated NCV of medial nerve and peroneal nerve among motor nerves; and medial nerve and sural nerve among sensory nerves. Rostock et al<sup>[14]</sup> evaluated NCV of only sensory neurons (medial nerve and sural nerve).







**3.6.3.** *AEs.* One of the 13 articles reported minor swelling and bruising at the site of acupuncture.<sup>[30]</sup> Four studies reported that there were no AEs associated with the intervention,<sup>[20,24,25,29]</sup> and 8 studies did not specify AEs.

## 4. Discussion

This review finally included 13 studies and synthesized the findings from 6 studies. The specific efficacy of acupuncture was not definitive because only 1 study compared EA and sham-EA. Three studies were designed to evaluate whether acupuncture could act as an adjuvant therapy to enhance the effectiveness of other therapies by comparing "conventional treatments" and "acupuncture plus conventional treatments;" however, the conventional treatments used differed between the studies, and therefore, their results could not be combined. Aside from 1 study using sham-EA as a control group, all 12 studies included acupuncture versus pharmacological treatments. The results showed that acupuncture could show a superior clinical efficacy than vitamin B therapy. However, the methodological quality of the involved studies was generally low.

We tried to collect quantitative data (scores) on symptoms such as pain, as a primary outcome, but only 2 studies reported VAS or NRS scores; therefore, the number of studies was not sufficient to synthesize the results. Considering that the clinical efficacy rates adopted in the 9 studies are nonquantitative and that each clinical study derived efficacy rates based on different criteria, the information can be merged in the meta-analysis, but the results must be interpreted cautiously.

Previous reviews addressed similar research questions. Most recently, Li et al<sup>[33]</sup> published a review on a quite similar topic. Although acupuncture is widely studied in China, the report published by Li et al did not included literature from Chinese databases; therefore, it included only 3 documents, which limited the analysis of results. Franconi et al<sup>[34]</sup> published a review in 2013, a time when few studies on acupuncture for the management/treatment of CIPN were available; therefore, there were significant limitations to the analysis of the results, such as analysis of case reports. However, since then, many studies have been published, and this review was conducted to analyze the effects of acupuncture.

The strength of this study is that literature published not only in English but also in Chinese and Korean, that is, languages that correspond to the countries that widely use acupuncture, was searched. Another strength is interpretation of results from RCTs. Furthermore, we applied stringent inclusion/exclusion criteria, and conducted meta-analysis using recognized tools to assess the quality of the studies included. Although the quality of the studies included was low, existing evidence on the effect of acupuncture on CIPN was systematically reviewed and analyzed.

The limitations of this study are mainly derived from the included studies. First, referring to the ROB summary, the quality of included studies was poor; therefore, careful interpretation is needed. Second, only 1 study compared the efficacy of EA and sham EA; therefore, the specific efficacy of acupuncture could not be elucidated. In addition, the method of acupuncture used in each of the included RCTs varied, and the number of RCTs included in this review was small, making it difficult to perform subgroup analysis based on different types of acupuncture methods.

#### 5. Conclusions

Acupuncture can be considered a safe treatment. The definitive efficacy of acupuncture for the treatment/management of CIPN could not be assured considering the methodological flaws of the included studies. Acupuncture has been shown to be more effective than vitamin B treatment in terms of clinical efficacy rate, but the interpretation of the results is limited by the use of different processes for deriving the efficacy rate. High-quality (low ROB) clinical studies that can be used as clinical basis for non-pharmacological therapies, such as acupuncture and EA for the treatment of CIPN, are needed.

## **Author contributions**

MSH and TYP designed the study. TYC, JHL, YSK, DCJ, and KSD developed the search strategy. MSH, HYL, and JHL wrote the manuscript and performed analysis. All authors provided critical revisions of the review and approved the final manuscript. Tae-Yong Park orcid: 0000-0002-6803-5483.

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