META-ANALYSIS

Collateral-Pricking and Bloodletting Cupping Combined with Electroacupuncture for Postherpetic Neuralgia: A Meta-Analysis

Yueyuan Yang, MM; Wenting Xu, MB; Mingzhu Li, MM; Yi Zhou, MM; Yu Qian, MM

ABSTRACT

Background • Acupuncture therapy has demonstrated significant efficacy in the treatment of postherpetic neuralgia, effectively alleviating pain intensity and enhancing patients' quality of life. However, the effectiveness of collateral-pricking and bloodletting cupping combined with electroacupuncture in the treatment of postherpetic neuralgia remains a subject of controversy. We aimed to assess the efficacy and safety of collateral-pricking and bloodletting cupping combined with electroacupuncture for postherpetic neuralgia.

Methods • We identified relevant randomized controlled trials by conducting a comprehensive search in multiple databases: China National Knowledge Infrastructure, China Biomedical Literature, Wanfang Data, PubMed, Cochrane Central Register of Controlled Trials, Embase, and Web of Science. The outcome included efficacy rate, visual analog scale (VAS)scores and pittsburgh sleep quality index (PSQI) scores. We meticulously assessed the risk of bias in the included trials and performed a meta-analysis.

Results • We analyzed 9 randomized controlled trials involving 639 patients. Collateral-pricking and bloodletting cupping combined with electroacupuncture achieved a significantly higher efficacy rate (risk ratio, 1.22 [95% CI, 1.13-1.31]; $P < .001$), reduced theVAS scores (standardized mean difference, −1.52 [95% CI, −2.26 to −0.79]; $P < .001$), and improved the PSQI scores (standardized mean difference, −2.31 [95% CI, −3.97 to −0.64]; $P = .007$) compared with the control groups. The subgroup analysis revealed that the combined treatment of collateral-pricking and bloodletting cupping and electroacupuncture had a significantly higher total effective rate compared with the carbamazepine, electroacupuncture, and pregabalin groups ($P < .05$). The total efficacy rate of the collateral-pricking and bloodletting cupping combined with electroacupuncture group was superior to that of the control group, irrespective of whether 2 or 3 courses were administered ($P < .05$).

Conclusion • Existing evidence suggests that the combination of collateral-pricking and bloodletting cupping and electroacupuncture demonstrates efficacy in pain relief, improvement of sleep quality, and enhanced therapeutic outcomes for patients with postherpetic neuralgia. However, further validation through large-scale multicenter randomized controlled trials is warranted due to the limited quantity and quality of the included literature in this study. (*Altern Ther Health Med.* [E-pub ahead of print.])

Yueyuan Yang, MM; **Wenting Xu**, MB; **Mingzhu Li**, MM; **Yi Zhou**, MM, Rehabilitation Department; Sanya Recuperation Center; Joint Logistics Support Force, People's Liberation Army; Sanya, Hainan Province; China; **Yu Qian**, MM, School of Health Medicine; Chongqing Youth Vocational and Technical College; Chongqing; China.

Corresponding author: Yu Qian, MM
E-mail: 17783437702@163.com
Corresponding author: Yi Zhou, MM
E-mail: 894763463@qq.com

INTRODUCTION

Varicella zoster virus causes chicken pox as a primary infection following which it becomes latent in neuron.[1,2] It may then reactivate to cause shingles. Postherpetic neuralgia (PHN), the most common sequela of shingles, is a chronic and refractory neuropathic pain syndrome.[3,4] It is characterized by persistent and intense pain in the region of nerves following the resolution of shingles lesions.[5] The annual incidence of PHN is approximately 3.9 to 42.0 cases per 100 000, and the incidence is positively correlated with age.[6] Women are more likely than men to develop shingles, and the annual incidence of shingles is approximately 0.3% to 0.5%, of which approximately 9% to 34% of patients with shingles will develop PHN.[7] The typical symptoms of PHN

are pronounced burning or electric shock-like sensations, paresthesia, or tearing pain localized to the areas where skin lesions manifested. Furthermore, these distressing physical manifestations are accompanied by negative affective states and sleep disturbances that significantly impede a patient's daily functioning.[8-10]

The primary pharmacological treatments for PHN consist of calcium-channel modulators such as pregabalin and gabapentin, tricyclic antidepressants such as amitriptyline, and 5% lidocaine patches.[11,12] The overall impact of these treatments is suboptimal, and prolonged use of the aforementioned medications may lead to adverse reactions such as dizziness, nausea, and abdominal discomfort.[13-15] The use of nerve blocks, surgical interventions, and other techniques can effectively and immediately mitigate the adverse effects of medications. However, these approaches have demanding requirements, high costs, require physicians trained in particular skills, require patient hospitalization and insufficient sustainability in terms of efficacy.[13,16] Hence, it is imperative to ascertain efficacious therapies for PHN that have minimal adverse effects.

Acupuncture therapy is a widely used complementary and alternative treatment that may be beneficial in managing PHN and includes acupuncture, electroacupuncture (EA), acupoint injection, collateral-pricking and bloodletting cupping (CPBLC), fire-needle therapy, and moxibustion.[17] Many experimental studies and extensive clinical practice have confirmed that acupuncture therapy exerts a positive on PHN.[18,19] CPBLC is an ancient and unique therapeutic method that involves puncturing the skin at diseased or specific acupoints to release a small amount of blood, followed by cupping, to completely eliminate stagnant blood from the body. It can enhance local microcirculation, decrease the concentration of pain-inducing substances, and effectively alleviate pain,[20,21] and is extensively used in the management of skin, inflammatory, and pain diseases.[22] EA is used to prevent and treat diseases by delivering microcurrents of electricity via acupuncture needles inserted into the body at acupuncture points after "de qi" (acupuncture needle sensation) is reported by patients. EA can effectively combine acupuncture stimulation with electrical stimulation, facilitate the recovery of damaged nerves, regulate neurotransmitter release in the body, suppress inflammatory-product secretion, enhance treatment efficacy, and, consequently, alleviate nerve pain.[23,24]

The findings of a comprehensive meta-analysis conducted by Cui, et al[16] demonstrated that the combination of CPBLC and antiepileptic drugs was more effective in alleviating pain associated with PHN compared with EA combined with antiepileptic drugs. Many studies have demonstrated that CPBLC combined with EA can significantly enhance the clinical efficacy of PHN treatment.[25-33] However, due to the inconsistencies in reported efficacy across various studies, the exact effectiveness lacks robust evidence-based support. Therefore, this study used a meta-analysis to assess the efficacy and safety of combining CPBLC with EA for PHN treatment, thereby aiming to provide evidential support for complementary and alternative approaches for managing PHN.

METHODS

This study strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[34]

Data sources and search strategies

We conducted a comprehensive literature search for randomized controlled trials that investigated the combined use of CPBLC and EA for treating PHN across multiple databases: China National Knowledge Infrastructure, China Biomedical Literature, Wanfang Data, PubMed, Cochrane Central Register of Controlled Trials, Embase and Web of Science. The literature search was limited to studies published prior to September 2023. We adjusted our search terms in accordance with each database's requirements and used a combination of Medical Subject Headings (MeSH) of the US National Library of Medicine terms and free-word searches. The search terms were as follows: *postherpetic neuralgia, PHN*, *electroacupuncture*, *cupping, cupping therapy,cupping therapies, cupping treatment, cupping treatments, bloodletting, bloodletting, blood-letting, pricking blood, collateral-pricking and bloodletting cupping.*

Eligibility criteria

We predefined the inclusion criteria following the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework for systematic reviews.

- Population: participants diagnosed with PHN without restrictions on age, sex, or nationality
- Intervention: CPBLC combined with EA
- Comparison: Western medicine and other acupuncture therapy
- Outcome: at least 1 of total response rate ([recovery + apparent + effective]/total number of cases × 100%), visual analog scale (VAS) score, and Pittsburgh sleep quality index score
- Study design: randomized controlled trials for PHN treated with CPBLC combined with EA

The predefined exclusion criteria were as follows:

- Duplicated literature
- Full text not available
- Literature with incomplete data or obvious errors
- Animal experiments, literature analysis, reviews, experience summaries, case reports, and similar

Trial selection

In accordance with the PRISMA flow chart, 2 researchers independently conducted a literature screening based on the predefined inclusion and exclusion criteria, with mutual verification. Any discrepancies were resolved through discussion or by involving a third investigator, ensuring a final consensus of at least 80%.

Data extraction

The data extraction table was designed in advance using Microsoft Excel for extracting information and cross-checking the results. The extracted data encompassed various elements such as title, author, year of publication, subject characteristics, intervention duration, intervention details, outcome indicators, and methodological quality of the included literature.

Quality assessment

The literature evaluation was conducted by 2 researchers in accordance with the Risk of bias tool (RoB2) in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.2.0.[35] The evaluation criteria were random sequence generation methods, assignment concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. These criteria were categorized as "low risk," "unclear," or "high risk." The aforementioned steps were independently carried out by both researchers and were cross-checked for consistency. Any discrepancies were resolved through discussion or were determined by a third researcher. A final agreement with no less than 80% consensus was required.

Data synthesis and analysis

RevMan software, version 5.3, was used to conduct a meta-analysis and to calculate 95% CIs and efficacy statistics of risk ratio for categorical variables and standardized mean difference for continuous variables. Heterogeneity among the included results was assessed using the χ^2 test, while the I^2 test quantitatively determined the extent of heterogeneity. If P was greater than or equal to .1 and I^2 was less than or equal to 50%, we concluded that there was no significant heterogeneity between different trials, and we selected a fixed-effect model. Conversely, if P was less than .1 and I^2 was greater than 50%, we concluded that there was high heterogeneity among different trials, and we selected a random-effects model. Subgroup analysis was performed based on the intervention course and different interventions in the control groups. Sensitivity analysis was carried out by a one-by-one exclusion method. Publication bias was evaluated using the Egger test and the Begg test.

RESULTS

Literature retrieval and characteristics

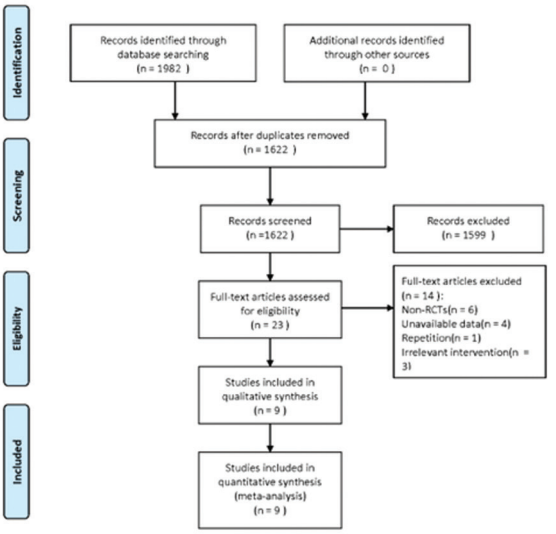
A total of 1982 literature sources were retrieved. After removing duplicates, 1622 sources were screened, and 1599 sources were excluded based on the evaluation of their titles and abstracts. The remaining 23 sources underwent thorough scrutiny during full-text reading, resulting in the exclusion of 14 additional sources. Finally, a total of 9 randomized controlled trials involving 639 patients were included in the meta-analysis (Figure 1).[25-33] The sample sizes of the included trials ranged from 60 to 94 patients. The treatment interventions used in the control groups were carbamazepine in 2 trials, EA in 3 trials, and pregabalin in 4 trials; 3 trials used 3 courses of intervention, while 6 trials used 2 courses of intervention. The basic characteristics of these 9 trials are presented in Table 1.

Table 1. Characteristics of the 9 Included Randomized Controlled Trials

Trial	Sample size		Age, mean (SD), y		Interventions		No. of courses	Outcomes
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group		
Qiao 2013[29]	32	31	51.6 (7.69)	55.7 (8.17)	CPBLC + EA	EA	2	①
Huang et al 2020[28]	45	45	65.8 (2.9)	65.9 (2.7)	CPBLC + EA	Pregabalin	3	①②
Wang 2019[30]	30	30	57.2 (9.65)	59.3 (11.03)	CPBLC + EA	EA	3	①②③
Wang 2023[31]	47	47	57.7 (5.21)	58.2 (5.34)	CPBLC + EA	Pregabalin	2	①②③
Chen 2020[26]	30	30	53.7 (5.18)	55.1 (4.85)	CPBLC + EA	Pregabalin	2	①②③
Chen 2010[25]	36	36	40 (≈75)	40 (≈72)	CPBLC + EA	Carbamazepine	3	②
He 2018[27]	40	40	44.3 (21.6)	39.7 (16.3)	CPBLC + EA	EA	2	②
Zhang et al 2021[32]	30	30	53 (9)	53 (10)	CPBLC + EA	Pregabalin	2	①②
Zhang 2018[33]	30	30	63.2 (4.07)	63.2 (4.16)	CPBLC + EA	Carbamazepine	2	②

Abbreviations: EA, electroacupuncture; CPBLC, collateral-pricking and bloodletting cupping; ①, Visual analog scale; ②, Total effective rate; ③, Pittsburgh sleep quality index.

Figure 1. Trial Selection Process



Abbreviation: RCT, randomized controlled trial.

Quality assessment of the trials

The results of bias risk assessment (illustrated in Figure 2) were as follows:

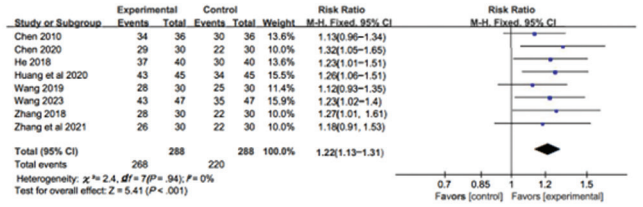
- Random sequence generation: 5 trials used the random number table method, while 4 trials mentioned "random" without specifying the specific randomization approach.
- Allocation concealment: 1 trial used allocation concealment, whereas it was unclear in the remaining trials.
- Blinding of participants and personnel: blinding was implemented in 1 trial, whereas it was unclear in the remaining trials.
- Blinding of outcome assessment: 1 trial achieved blinding, whereas it was unclear in the remaining trials.
- Incomplete outcome data: low risk of bias.
- Selective reporting: low risk of bias.
- Other bias: low risk of bias.

Figure 2. Risk of Bias Summary

Study	①	②	③	④	⑤	⑥	⑦
Chen 2010[25]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Chen 2020[26]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
He 2018[27]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Huang et al2020[28]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Qiao 2013[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wang 2019[30]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Wang 2023[31]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Zhang 2018[32]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Zhang et al 2021[33]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk

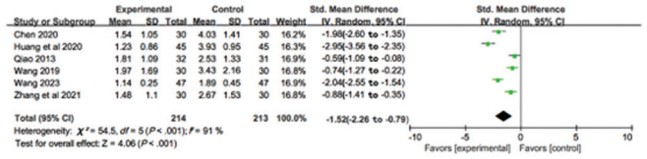
Abbreviations: ①Random sequence generation (selection bias); ②Allocation concealment (selection bias); ③Allocation concealment (selection bias); ④Allocation concealment (selection bias); ⑤Incomplete outcome data (attrition bias); ⑥Selective reporting (reporting bias); ⑦Other bias.

Figure 3. Total Effective Rate



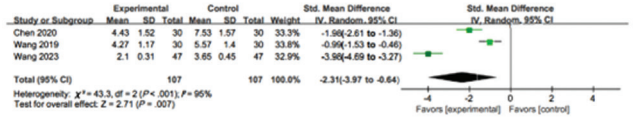
Abbreviations: RR, risk ratio; Std, standard deviation;M-H, Mantel-Haenszel; df, degree of freedom

Figure 4. Visual Analog Scale Scores



Abbreviation: RR, risk ratio; Std, standard deviation; IV, Inverse Variance;df, degree of freedom

Figure 5. Pittsburgh Sleep Quality Index Scores



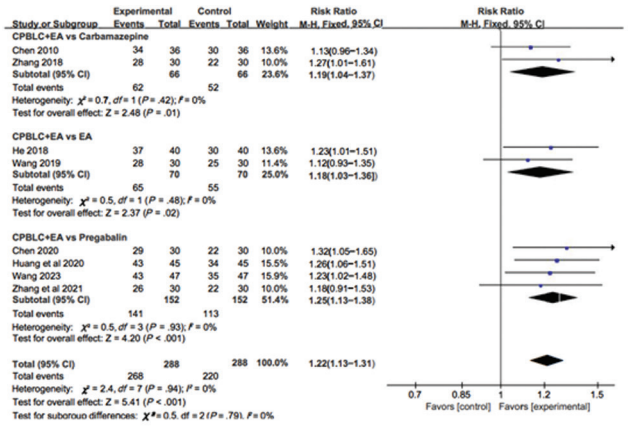
Abbreviations: Std, standard deviation; IV, Inverse Variance; df, degree of freedom.

Results of meta-analysis

Total effective rate. This analysis included 8 trials. The meta-analysis using a fixed-effect model demonstrated that the combined treatment of CPBLC and EA exhibited a significantly higher total effective rate compared with the control group (risk ratio, 1.22 [95% CI, 1.13-1.31]; $P < .001$) (Figure 3).

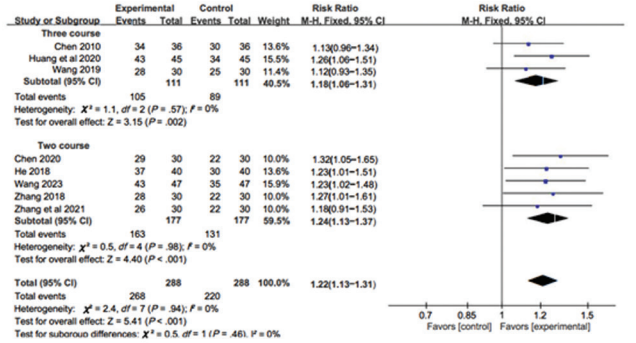
VAS scores. This analysis included 6 trials. The meta-analysis using a random-effects model demonstrated that the combination of CPBLC and EA was associated with a significant reduction in VAS scores in patients with PHN compared with Western medicine treatment groups(standardized mean difference, −1.52 [95% CI, −2.26 to −0.79]; $P < .001$) (Figure 4).

Figure 6. Subgroup Analysis of Different Interventions in the Control Groups



Abbreviations: RR, risk ratio;M-H, Mantel-Haenszel; df, degree of freedom

Figure 7. Subgroup Analysis of Different Treatment Courses



Abbreviations: RR, risk ratio; M-H, Mantel-Haenszel; df, degree of freedom.

Pittsburgh sleep quality index scores. This analysis included 3 trials. Meta-analysis using the random-effects model demonstrated that combining CPBLC with EA could significantly enhance Pittsburgh sleep quality index scores in patients with PHN compared with Western medicine treatment groups(standardized mean difference, −2.31 [95% CI, −3.97 to −0.64]; $P = .007$) (Figure 5).

Subgroup analysis

Subgroup analysis was conducted based on the intervention course and different interventions in the control groups. The subgroup analysis revealed that the combined treatment of CPBLC and EA had a significantly higher total effective rate compared with the carbamazepine, EA, and pregabalin groups ($P < .05$) (Figure 6). The total efficacy rate of the CPBLC combined with EA group was superior to that of the control group, irrespective of whether 2 courses or 3 courses were administered ($P < .05$) (Figure 7).

Sensitivity analysis

The robustness of the total effective rate findings was assessed by sensitivity analysis, which was consistent with the meta-analysis results (Figure 8).

Figure 8. Sensitivity Analysis of Total Effective Rate

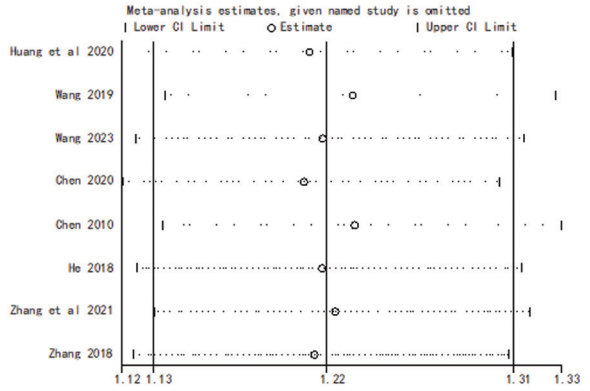
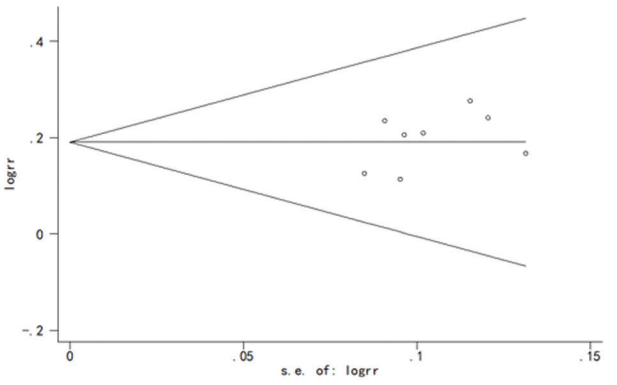


Figure 9. Publication Bias of Total Effective Rate



Abbreviation: RR, risk ratio.

Publication bias

Analysis of publication bias was conducted using the overall efficacy rate, and there were no indications of publication bias (Egger $P = .29$; Begg $P = .46$) (Figure 9).

DISCUSSION

PHN is frequently accompanied by sleep disorders, and optimal sleep quality is crucial for patients' recovery.[36] The commonly used pharmacotherapies include calcium-channel modulators such as pregabalin and tricyclic antidepressants; however, a significant number of patients still fail to achieve satisfactory outcomes.[21,37] Acupuncture therapy is considered potentially advantageous in the management of neuropathic pain and generally poses no safety concerns.[38,39] In clinical treatment of PHN, there exists a variety of available acupuncture techniques,[40-43] with several trials reporting the combined use of 2 or more methods.[41,44,45] The clinical practice guidelines for acupuncture recommend the use of fire needles, EA, and CPBLC for PHN and suggest that a combination of 2 or more of these methods yields enhanced therapeutic benefits.[46] We aimed to assess the efficacy and safety of CPBLC combined with EA for postherpetic neuralgia.

A total of 9 randomized controlled trials were included in this meta-analysis, involving 639 patients. The meta-analysis findings demonstrated statistically significant reduction in patients' VAS scores, improvement in sleep quality, and enhanced treatment outcomes with the combination of CPBLC and EA. CPBLC and EA, as acupuncture therapies, synergistically enhance each other's therapeutic effects, providing patients with superior options for pain relief and sleep improvement while improving overall treatment efficacy. This finding holds great significance for improved patient recovery and quality of life.

Numerous meta-analyses pertaining to the acupuncture treatment of PHN have been published worldwide.[8,13,16,19] The intervention groups primarily received a combination of acupuncture treatments, while the control groups underwent Western medicine treatment. The findings from these studies consistently demonstrate that each acupuncture modality is an effective and safe therapeutic approach for PHN, which aligns closely with the results obtained in this study. A meta-analysis conducted by Cui et al[16] demonstrated that the combination of CPBLC and antiepileptic drugs had the highest efficacy as an acupuncture-based pain-relief technique, whereas EA in combination with antiepileptic drugs proved to be the most effective acupuncture-related approach for alleviating symptoms of insomnia and depression associated with PHN. Subgroup analysis revealed that CPBLC combined with EA surpassed both Western medicine and EA therapy in terms of effectiveness, pain reduction, and improvement in sleep quality. Pei et al[19] demonstrated that both CPBLC and EA yielded superior effects in relieving pain intensity, which aligns with the findings of this study. Acupuncture is increasingly being used to treat PHN. In comparison with conventional Western medicine, acupuncture exhibits fewer side effects, a shorter treatment duration, higher efficacy, and enhanced safety.[28]

CPBLC and EA are commonly used in traditional Chinese medicine and are used extensively in clinical practice. EA, a commonly used analgesic therapy in acupuncture therapy, is believed to stimulate the release of opioid peptides, modulate nerve-conduction velocity, and regulate anti-inflammatory factors and pro-inflammatory cytokines, among other mechanisms, so as to achieve a more optimal analgesic effect.[47] CPBLC for treating PHN primarily facilitates the elimination of local inflammatory toxins within the skin, accelerates local metabolism, and stimulates nerve impulses to suppress pain, thereby exemplifying the interconnectedness of the neuro-immune-endocrine network.[30] CPBLC enhances local blood circulation, augments the delivery of oxygen and nutrients, and expedites the process of tissue repair and rehabilitation.[29] CPBLC can also enhance the conduction channels for EA stimulation by facilitating the flow of qi and blood (2 basic bodily fluids in Chinese medicine) along the meridians.[26] This can augment the stimulatory effect of EA and enhance treatment efficacy, while concurrently modulating nervous-system function to potentiate the therapeutic impact of CPBLC. This integrated approach alleviates symptoms and mitigates patient discomfort. The Jiaji (EX-B 2) acupuncture point is susceptible to invasion by the herpes virus due to its anatomical association with the spinal nerve and the

sympathetic nerve.[45] EA can stimulate the Jiaji (EX-B 2) point and can inhibit central signal transmission at the spinal-cord level so as to exert an analgesic effect.[26] Our meta-analysis results showed that the combination of CPBLC and EA significantly reduced patients' VAS scores, improved sleep quality, and enhanced treatment outcomes. The mechanism underlying this combined therapy primarily regulates the functions of the meridian, nervous, immune, and endocrine systems. However, further investigations are warranted to substantiate these mechanisms and to explore additional pathways influenced by CPBLC combined with EA therapy. This will enhance our comprehension of the treatment mechanism associated with traditional Chinese medicine therapy and facilitate the development of more efficacious clinical strategies.

This study has several notable : First, it is the pioneering meta-analysis of randomized controlled trials investigating the combined use of CPBLC with EA for treating PHN. Consequently, this study will provide substantial empirical evidence supporting the efficacy and viability of complementary and alternative therapies in managing PHN. Second, apart from assessing overall efficacy, this study also evaluated patients' VAS scores and placed emphasis on Pittsburgh sleep quality index scores. As a result, a more comprehensive evaluation of the therapeutic effects of combining CPBLC with EA can be achieved, thereby providing greater clinical reference value. Third, by conducting subgroup analyses based on intervention course and different interventions in the control groups, this study demonstrated that CPBLC combined with EA surpasses other treatment modalities and yields rapid improvements in treatment outcomes. Fourth, the meta-analysis techniques used in this study allowed us to observe significant therapeutic effects across multiple independent studies involving CPBLC combined with EA. The consistency found among these studies enhances both the reliability and generalizability of our results while endorsing CPBLC combined with EA as an effective complementary and alternative therapy.

There were some limitations to this study: First, 4 trials mentioned randomization but did not provide a detailed description of the randomization method; and only 1 trial mentioned allocation concealment. This lack of information regarding the randomness of clinical trials may lead to potential selective bias. Second, the Pittsburgh sleep quality index and VAS scores showed significant heterogeneity, which could be attributed to potential biases in the included trials, variations in acupuncture-point selection, and differences in treatment duration. Third, the limited number of included trials undermined the reliability of the results. Fourth, the inclusion of trials with small sample sizes further amplifies the potential for bias.

CONCLUSION

In conclusion, the combination of CPBLC and EA demonstrates efficacy in pain relief, improvement of sleep quality, and enhanced therapeutic outcomes for patients with PHN. Nevertheless, it is crucial to acknowledge the limitations of this study, emphasizing the need for further large-scale randomized controlled trials to validate these findings and provide robust evidence supporting their implementation in clinical practice.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

Yueyuan Yang and Yu Qian: conception and design, and drafting and writing. Yueyuan Yang, Wenting Xu, Mingzhu Li, Yi Zhou, and Yu Qian: retrieval and screening of studies, and extraction of data. Yueyuan Yang and Wenting Xu: evaluation of the methodological quality of included studies. Mingzhu Li, Yi Zhou, and Yu Qian: statistical analysis. Yueyuan Yang and Yu Qian: revision of chart. Yueyuan Yang, Wenting Xu, and Yu Qian: review and revision. All authors contributed to the article and approved the submitted version.

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Yueyuan Yang, MM, and Wenting Xu, MB, contributed equally to this work and are co–first authors.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in this article. Further inquiries can be directed to the corresponding authors.

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