

## **Review** Article

# Efficacy and Safety of Electroacupuncture for Pain Control in Herpes Zoster: A Systematic Review and Meta-Analysis

Kelin He<sup>1,2</sup> Fengjia Ni,<sup>1,2</sup> Yi Huang,<sup>2</sup> Mengyi Zheng,<sup>2</sup> Han Yu,<sup>2</sup> Dexiong Han,<sup>1</sup> and Ruijie Ma<sup>1,2</sup>

<sup>1</sup>Department of Acupuncture and Moxibustion, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

<sup>2</sup>The Third School of Clinical Medicine (School of Rehabilitation Medicine), Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Correspondence should be addressed to Ruijie Ma; maria7878@sina.com

Received 4 March 2022; Revised 2 June 2022; Accepted 13 June 2022; Published 4 July 2022

Academic Editor: Cheng-Hao Tu

Copyright © 2022 Kelin He et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction. Herpes zoster is caused by the reactivation of the latent varicella-zoster virus, which leads to acute pain that may disturb routine activities and affect patients' quality of life. Electroacupuncture (EA) has been commonly used for treating herpetic pain in clinical treatment. However, no relevant studies have been performed to evaluate the efficacy and safety of EA for acute control in herpetic neuralgia patients. The purpose of the current study was to conduct a systematic review and meta-analysis to address the deficiencies of the current research. Methods. Three English (PubMed, Cochrane Library, and Web of Science) and four Chinese (China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature database (CBM), Wan-fang database, and the Chinese Scientific Journals Full-text Database (VIP)) were comprehensively searched from inception to 31 December 2021. Two independent reviewers evaluated the retrieved data based on the eligibility criteria in advance. In addition, the Cochrane Risk of Bias Tool was used to assess the methodological quality of the included studies. Outcome indexes in this study included the visual analog scale, the time to cessation of pustules, the time to scabs, the time to rash healing, adverse reactions, and the incidence of postherpetic neuralgia. Sensitivity and subgroup analyses were also performed to evaluate the intervention effect specifically. In addition, publication bias was analyzed. Results. Six randomized controlled trials (167 participants in the experimental groups and 174 participants in the control groups) were identified as reporting the application of EA for acute herpes zoster pain and were included in this study. The results from our meta-analysis revealed that EA was superior to control treatment according to visual analog scale, the time of rash healing, and the incidence of postherpetic neuralgia. However, in terms of the time to cessation of pustules, scabs, and adverse reactions, the results showed that EA compared with the control group showed no significant difference. In addition, subgroup analyses indicated that 2/100 Hz-EA has more significant effects on herpetic pain. Sensitivity analyses revealed that the results of EA for acute pain control and the rash healing time in herpetic neuralgia patients were stable. However, a publication bias was observed. Conclusion. Our meta-analysis results showed that EA could offer certain advantages in treating acute pain in herpetic neuralgia patients. However, small sample sizes, heterogeneity in study design, and variable methodological quality weaken these inferences. In addition, weak evidence was found for the safety of EA.

## 1. Introduction

Acute herpes zoster pain is a feared disease caused by reactivation of the latent varicella-zoster virus located in the spinal or cranial sensory ganglia and usually occurs decades after the primary infection. It is mainly characterized by burning, shooting (like an electric shock), or intolerable pruritus in constant association with the outbreak of vesicular skin rash. [1–3] Moreover, these symptoms can severely influence the physical and mental health of patients, as well as their quality of life. An early study shows that herpes zoster commonly occurs in older patients, and herpes zosterassociated mortality increases with age. [4] Currently, early treatment with antiviral drugs such as acyclovir and vidarabine shortens the duration of skin lesions related to herpes zoster. [5] In terms of acute pain control in herpetic neuralgia patients, there is still no good management for treating this condition. Although nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and sympathetic nerve blockers are used to manage herpetic neuralgia, these treatments do not permanently alleviate severe pain. [6] But these drugs, even though effective, have more troubling adverse effects. In addition, early aggressive therapy is an important step forward for preventing postherpetic neuralgia. [7, 8] Therefore, developing new therapeutic strategies for treating acute pain in herpetic neuralgia patients is urgently needed.

As a vital part of complementary and alternative medicine, acupuncture has been widely applied in clinical practice. Previous studies have shown that acupuncture can treat various acute and chronic pain. [9, 10] Different acupuncture methods include manual acupuncture, electroacupuncture (EA), warm needling, auricular therapy, fire needling, etc., Currently, EA is one of the most common methods for treating pain in traditional Chinese medicine hospitals and has an excellent therapeutic effect on acute and chronic pain. [11-13] Recent studies have shown that EA can relieve pain by activating numerous bioactive chemicals through peripheral and central mechanisms and forestall the adverse impacts of often-debilitating pharmaceuticals. [14] Over recent years, some studies have confirmed that EA effectively relieves postherpetic neuralgia. [15, 16] However, the current state of evidence of EA for treating acute pain in herpetic neuralgia patients has been so far unknown. Therefore, this study aimed to answer these questions by conducting a systematic review and meta-analysis.

#### 2. Methods

2.1. Design. This present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17], and the study protocol has been registered on PROSPERO (Registration number: CRD42021297341).

2.2. Search Strategy. We had systematically searched the following seven electronic databases from inception to 31 December 2021: PubMed, Cochrane Library, Web of Science, CNKI, CBM, Wan-fang database, and VIP, to identify all the randomized controlled trials (RCTs) on EA for the treatment of acute pain in herpetic neuralgia patients. In addition, postgraduate theses or dissertations were also eligible. The following terms were searched as subject words, keywords, free-text terms, and MeSH terms: herpes zoster, shingles, herpetic neuralgia, acupuncture, acupuncture therapy, electroacupuncture. Apart from the above, there were no language, region, or countries restrictions.

2.3. Eligibility Criteria. This study included all available RCTs of EA for the treatment of acute pain in herpetic neuralgia patients. Any other types of literature such as

system reviews, letters, case reports, editorials, animal studies, commentary, and non-RCTs were to be excluded.

2.4. Participants. Literature was included in which adult participants (older than 18 years) were diagnosed with herpetic neuralgia. All patients were in the acute phase of the disease (less than two weeks) and had not yet been treated.

2.5. Interventions. The intervention in the experimental group included EA alone or in combination with routine treatment (RT), and the control group included RT and/or sham EA.

2.6. Outcomes. The primary outcome indicator of this study was the pain severity, and the secondary outcome indicators included the time to cessation of pustules, the time to scabs, the time to rash healing, adverse reactions, and the incidence of postherpetic neuralgia.

2.7. Literature Selection and Data Extraction. One reviewer performed literature searches according to specified searching strategies and downloaded the related citations. All literature were imported into Endnote X9 software, and the duplicate literature was removed using electronic/ manual checking. Subsequently, two independent reviewers screened and identified the titles and abstracts of the remaining literature, and then, independently retrieved the literature that fulfilled the inclusion criteria. Discussion or involving the corresponding author resolved any inconsistent result between reviewers. After initial screenings, two reviewers extracted data independently from the identified studies. The following information was extracted from each study: general information (authors, publish year), demographic data (sample size, intervention, age, sex), EA protocol (acupoints, acupuncture modality, retention time, and treatment duration), and outcome measure.

#### 2.8. Data Analysis

2.8.1. Assessment of Risk of Bias in Included Studies. Two independent reviewers evaluated the risk of bias of each study by using the Cochrane risk of the bias assessment tool. [18] This assessment tool mainly includes seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain of the individual study was classified as high, low, or unclear risk. Discussions with the corresponding author resolved any discordance between the two reviewers.

2.8.2. Statistical Analysis. All data analyses of this study were conducted with R software (version 3.6.3; package meta). Continuous variables were calculated as mean differences (MD) and at 95% confidence interval (CI). If the unit of MD varied between studies, standardized MD (SMD)



FIGURE 1: Flow diagram depicting the selection process of eligible studies. (CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journals Full-Text Database; SinoMed, the Chinese Biomedical Literature Database; *n* number of publications).

was calculated. The random or fixed effects model was based on the clinical and methodological heterogeneity among the studies pooled in a meta-analysis. [19] The  $I^2$  statistic was used to evaluate the statistical heterogeneity of the studies (with  $I^2$  statistic > 50% indicating statistically significant heterogeneity). [20] In addition, sensitivity analyses and subgroup analyses were carried out to dissect the heterogeneity.

#### 3. Results

3.1. Literature Selection. In total, 1956 published references were initially identified (399 references from CNKI, 438 references from Wan-fang, 247 references from VIP, 499 references from SinoMed, 136 references from PubMed, 77 references from Cochrane Library, and 160 references from Web of Science) and imported into Endnote X9. After eliminating duplicates, 741 articles were retained. We excluded reviews, case reports, animal experiments, and other irrelevant studies from these, and 14 studies remained. Moreover, mixed interventions, non-randomized methods, data missing, and outcome indicators that did not include

outcomes were excluded. Finally, six studies were considered after full-text reading. The detailed flowchart of the literature screening process is shown in Figure 1.

3.2. Characteristics of Included Studies. A total of six articles were included, consisting of 341 participants with acute pain in herpetic neuralgia (n = 174 for the control group; n = 167 for the experimental group). The interventions in the control group included RT only, and the interventions in the experimental group were RT + EA or EA only. For outcome measure, six trials involved a visual analog scale, three involved times to cessation of pustules, scabs, and rash healing, and two reported adverse reactions and incidence of postherpetic neuralgia. The detailed characteristics of included studies are shown in Table 1.

*3.3. Risk of Bias Assessment.* Figure 2 summarizes the risk of bias of the included studies. Regarding the random sequence generation, two trials [22, 26] reported the sequence generation method and were assessed as low risk of bias; three trials [21, 23, 24] only mentioned random but no specific method

		Int	ervention	Age (	(years)	Sex	(M/F)	Disease cou	urse (days)	Outcome meaning
C	C		Ε	С	Ε	С	Ε	С	С	Outcome measure
alaciclovir, 300 mg, orally three times daily EA: EA on the Jia 1 days: vitamin B1, 10 mg, orally three times 3); sparse and den daily for ten days was 30 minutes,	lovir, 300 mg, orally three times daily EA: EA on the Jia ; vitianin B1, 10 mg, orally three times 33; sparse and den daily for ten days was 30 minutes,	EA: EA on the Jia 3); sparse and dens was 30 minutes,	ji (EX-B2) + Zhigou (TE6) + Houxi (SI se waves (2/100 Hz), treatment duration once a day for ten consecutive days.	43.47 ± 13.57	$42.23 \pm 14.98$	15/15	16/14	$4.77 \pm 1.76$	5.10 ± 1.45	VAS, the time to cessation of pustules, scabs, rash healing, the incidence of noschemetic norralora
alacidovir, 300 mg, orally twice daily for ten $EA$ : EA on the a vitamin B1, 10 mg, orally three times daily treatment duratic for ten days	lovir, 300 mg, orally twice daily for ten $EA$ : EA on the a $0$ + Houxi (SI 3) in B1, 10 mg, orally three times daily treatment duratic for ten days	EA: EA on the a 6) + Houxi (SI 3) treatment duratic	shi points + Jiaji (EX-B2); Zhigou (TE ); sparse and dense waves (2/100 Hz), on was 30 minutes, once a day for ten consecutive days.	49.61 ±16.34	$48.39 \pm 17.06$	24/7	16/11	4.87 ± 2.25	$5.25 \pm 2.01$	VAS, the time to cessation of pustules, scabs, rash healing, and the incidence of postherpetic neuralgia
Indomethacin, 25 mg, three times daily for $RT + EA$ . EA of days valaciclovir, 300 mg, orally twice daily (LR3), continue even days: vitamin B1, 10 mg, orally three minutes for 2011 <sup>12</sup> times daily for seven days once a day once a day	tethacin, 25 mg, three times daily for $RT + EA$ . EA or valaciclovit; 300 mg, orally twice daily (LR3), continue lays, vitamin B1, 10 mg, orally three minutes for 201121 times daily for seven days once a d	RT + EA: EA of Yanglingquan ( (LR3), continu, minutes for 20 Hz once a da	n the Hegu (LI4) + Waiguan (TE 5); (GB34) + Zulinqi (GB41) + Taichong use-wave (20 minutes for 80 Hz, 10 3), treatment duration was 30 minutes, yf for seven consecutive days.	18-45: 7 persons; 46-60: 6 persons; 60-80: 14 persons	18–45: 9 persons; 46–60: 8 persons; 60–80 : 10 persons	13/14	14/13	Less than one week	Less than one week	SAV
Didofenac, 75 mg, orally once daily for ten s mecobalamin, 05 mg, orally hrete times or ten days; valacidovir, 250 mg, orally hree for ten days external 3% boric acid solution for ten days external 3% boric acid solution	enac. 75 mg, orally once daily for ten RT + EA: EA on Obalamin, 0.5mg only three times (60 H2), treatment days; valaciclovir, 250mg, orally three internal 3% boric acid solution for targs external 3% boric acid solution	RT + EA: EA on (60 Hz), treatment for	the Jiaji (EX-B2), continuous wave duration was 30 minutes, once a day ten consecutive days.	$47.14 \pm 10.34$	$47.28 \pm 10.41$	5/7	6/7	Not mentioned	Not mentioned	VAS, the time to cessation of pustules, scabs, and rasl healing
Valaciclovir, 0.3g, orally twice daily for 14 RT+EA. (EA on th s adenosylcobalamin, 0.5 mg, orally three continuous-wave for 14 days; pregabalin, 150 mg, orally twice minutes, once daily for 14 days	clovir, 0.3g, orally twice daily for 14 RT+EA: (EA on th aosylcobalamin, 0.5 mg, orally three continuous-wave days; pregabalin, 150 mg, orally twice minutes, once daily for 14 days	RT + EA: (EA on th continuous-wave minutes, once	e Jiaji (EX-B2) + local points of rash, (2Hz), treatment duration was 30 a day for 14 consecutive days.	$56.53 \pm 9.15$	57.89 ± 8.22	22/23	20/25	Less than one week	Less than one week	VAS
'alaciclovir, 0.3 g, orally twice daily for ten methylcobalamin, 0.5 mg, orally three times n days. If the pain were swere, oxycodone (10 mg) would be used.	clovir, 0.3 g orally twice daily for ten (scobalamin, 0.5 mg, orally three times (if the pain were severe, oxycodone (0 mg) would be used.	RT + EA: EA on continuous-wave minutes, onc	the Jiaji (EX-B2) + local ashi points, e (2 Hz), treatment duration was 30 e a day for ten consecutive days	61.1 ±2.13	$51.40 \pm 3.12$	17/12	12/13	$4.72 \pm 0.38$	$4 \pm 0.36$	VAS, the incidence of postherpetic neuralgia

TABLE 1: Characteristics of included studies.



(b)

FIGURE 2: Bias risk assessment. (a) Risk of bias summary; (b) Risk of bias graph.

and was rated as unclear risk; one trial [25] did not mention randomization and was assessed as high risk. Concerning allocation, one study [22] provided the allocation concealment method in detail and was considered to be at a low risk of bias; five trials [21, 23–26] were rated as unclear risk of bias resulting from insufficient detail in the studies. For blinding of participants and personnel, six articles [21–26]were ranked as high risk of bias resulting from EA (a treatment) of procedural nature. Regarding the blinding of outcome assessments, six trials [21–26] were rated as high risk of bias because of no data regarding the assessment process. In terms of incomplete outcome data, five trials [21, 22, 24–26] recorded all results and were rated as low risk of bias; one trial [23] was unclear because they reported insufficient details to ensure that the baseline was balanced after dropping out. In terms of selective reporting, six studies [21–26] reported all data and were rated as low risk of bias. In addition, five trials [21, 22, 24–26] did not appear to any other potential sources and were assessed as low risk of bias; one article [23] was classified as an unclear risk due to insufficient details after patients dropped out of the trials.

#### 3.4. Meta-Analysis Results

3.4.1. The Pain Severity. All studies reported pain severity. After carefully reading the full text of corresponding studies, four trials used a visual analog scale (0–10 point), and two trials used another visual analog scale (0–100 point). Hence, SMD was calculated for the meta-analysis. The results of  $I^2$  statistic > 50%, the random-effect model was used to

Study	Exper Total	imental Mean	group SD	Co Total	ntrol gr Mean	oup SD	Standardised Mean Difference	SMD	95%-CI	Weight %
Song2009	30	2.60	4.9500	30	22.17	12.7800		-1.99	[-2.62; -1.37]	17.7
Li2011	27	3.21	8.5300	31	15.19	15.5600		-0.92	[-1.47; -0.38]	18.1
Lin2015	27	1.48	0.9400	27	3.22	0.6400		-2.13	[-2.81; -1.45]	17.5
Lu2017	13	2.05	0.1800	12	4.15	0.5700	;	-4.89	[-6.57; -3.22]	11.9
Wei2019	45	1.58	1.2100	45	2.77	1.7700	·	-0.78	[-1.21; -0.35]	18.5
Cheng2018	25	1.32	0.2870	29	2.59	0.4020		-3.53	[-4.40; -2.65]	16.4
Random effects model	167			174			↓	-2.20	[-3.13; -1.27]	100.0
Hetrogeneity: $I^2 = 91\%$	$t_{0}^{2}$ , $\tau^{2} = 1$	.1684, j	0.01				-6 -4 -2 0 2 4 6			

						(a	)			
Study	Exper Total	imental Mean	l group SD	Co Total	ntrol gr Mean	oup SD	Standardised Mean Difference	SMD	95%-CI	Weight %
subgroup = 2/100Hz										
Song2009	30	2.60	4.9500	30	22.17	12.7800		-1.99	[-2.62; -1.37]	25.0
Li2011	27	3.21	8.5300	31	15.19	15.5600		-0.92	[-1.47; -0.38]	25.6
Random effects model Hetrogeneity: $I^2 = 84\%$	$57$ , $\tau^2 = 0$	0.4815,	p = 0.01	61			-	-1.45	[-2.49; -0.40]	50.6
<i>subgroup = 2Hz</i> Wei2019 Cheng2018	45 25	1.58 1.32	1.2100 0.2870	45 29	2.77 2.59	1.7700 0.4020		-0.78 -3.53	[-1.21; -0.35] [-4.40; -2.65]	26.3 23.0
Random effects model Hetrogeneity: $I^2 = 97\%$	$70, \tau^2 = 3$	3.6584, j	p < 0.01	74				-2.13	[-4.82; 0.57]	49.4
Random effects model Hetrogeneity: $I^2 = 92\%$ Residual hetrogeneity:	127 $\tau^2 = 1$ $I^2 = 95$	1.0100, j 5%, <i>p</i> <	p < 0.01 0.01	135			-4 -2 0 2	-1.75 	[-2.79; -0.72]	100.0

(b)

FIGURE 3: Funnel plot of the pain severity. (a) Standardized mean differences of VAS with experimental group compared with the control group. (b) Subgroup analyses.

perform the meta-analysis. Results showed that EA compared with no EA showed a significant difference (SMD = -2.20, 95% CIs = -3.13; -1.27), which is presented in Figure 3(a). Subgroup analysis results showed that 2/ 100 Hz had a positive effect size (SMD = -1.45, 95% CIs = -2.49; -0.40) (Figure 3(b)). In addition, sensitivity analysis indicated that the results of this meta-analysis were reliable and robust after excluding studies one by one (details in Supplementary Material, FS1).

3.4.2. The Cessation of Pustules Time. Among these studies, three studies involved the time to cessation of pustules. The definition of the cessation of pustules time is as follows: the time from the start of treatment until the blisters stop growing. Heterogeneity was significant ( $I^2$  statistic > 50%); therefore, the random effects model was used to perform the meta-analysis. The meta-analysis results showed that EA compared with no EA showed a significant difference (MD = -2.02, 95% CIs = -3.81; -0.23), which is presented in Figure 4. In addition, sensitivity analysis showed that the meta-analysis result was not stable. The sensitivity analysis was performed by sequentially deleting each original article.

The results suggested that the main factors affecting the stability of outcomes were the studies conducted by Song [21] and Lu [24] (details in Supplementary Material, FS2).

3.4.3. The Time to Scab. Among these studies, three studies reported the time to scabs. Heterogeneity was significant ( $I^2$  statistic > 50%), and random effects model was used to perform the meta-analysis. The results of this meta-analysis showed that EA compared with no EA showed no significant difference (MD = -2.69, 95% CIs = -5.42; 0.04), which is presented in Figure 5. In addition, sensitivity analysis revealed that the meta-analysis result was not stable. The sensitivity analysis was performed by sequentially deleting each original article. The results suggested that the main factors affecting the stability of outcomes were the studies conducted by Song [21] and Lu [24] (details in Supplementary Material, FS3).

3.4.4. The Rash Healing Time. Among these studies, only three trials provided the time to rash healing. Heterogeneity was significant ( $I^2$  statistic > 50%), therefore, the random effects model was applied. The results of this meta-analysis showed that EA compared with no EA showed a significant

Study	Exper Total	imental Mean	group SD	Co Total	ntrol gr Mean	roup SD	Mear Differe	n nce		MD	95%-CI	Weight %
Song2009	30	5.63	1.7300	30	8.43	2.4300				-2.80	[-3.87; -1.73]	33.1
Li2011	27	4.78	2.3800	31	4.91	1.8800				-0.13	[-1.25; 0.99]	32.8
Lu2017	13	4.01	1.1200	12	7.10	1.2500				-3.09	[-4.02; -2.16]	34.1
Random effects model Hetrogeneity: $I^2 = 89\%$	$70$ , $\tau^2 = 2$	2.2244, j	<i>v</i> < 0.01	73						-2.02	[-3.81; -0.23]	100.0
0 /							-4 -2 (	0 2	4			

FIGURE 4: Funnel plot of the cessation of pustules time.

Study	Exper Total	imental Mean	group SD	Co Total	ntrol gr Mean	oup SD	Mean Difference	MD	95%-CI	Weight %
Song2009	30	6.83	1.9500	30	11.70	4.7900		-4.87	[-6.72; -3.02]	32.2
Li2011	27	7.89	3.0200	31	7.85	3.1500		0.04	[-1.55; 1.63]	33.5
Lu2017	13	7.41	2.0900	12	10.72	1.4500		-3.31	[-4.71; -1.91]	34.3
Random effects model Hetrogeneity: $I^2 = 88\%$	$70, \tau^2 = 5$	5.1376, j	<i>p</i> < 0.01	73				-2.69	[-5.42; 0.04]	100.0
							-6 -4 -2 0 2 4 6			

FIGURE 5: Funnel plot of the time to scab.

Study	Exper Total	imental Mean	group SD	Co Total	ntrol gr Mean	oup SD	Mean Difference		MD	95%-CI	Weight %
Song2009	30	15.53	6.0300	30	27.23	10.3600			-11.70	[-15.99; -7.41]	27.6
Li2011	27	17.44	6.9700	31	22.00	7.2400			-4.56	[-8.22; -0.90]	31.3
Lu2017	13	11.98	2.8400	12	18.52	2.5600			-6.54	[-8.65; -4.42]	41.1
Random effects model Hetrogeneity: $I^2 = 69\%$	$70, \tau^2 = 6$	5.2682, j	b = 0.04	73					-7.35	[-10.77; -3.92]	100.0
		_					-15 -10 -5 0 5 1	0 15			

FIGURE 6: Funnel plot of the rash healing time.

Study	Experime Events	ntal group 5 Total	Contro Events	ol group 5 Total		(	Odds Rati	0		OR	95%-CI	Weight %
Song2009	0	30	4	30						0.10	[0.00; 1.88]	54.5
Li2011	0	27	1	27						0.32	[0.01; 8.24]	45.5
Cheng2018	0	25	0	29			-					0.0
Random effects mo	del	82		86	-					0.17	[0.02; 1.49]	100.0
Hetrogeneity: $I^2 = 0$	$0\%, \tau^2 = 0,$	p = 0.59				1						
					0.01	0.1	1	10	100			

FIGURE 7: Funnel plot of the safety outcome.

difference (MD = -7.35, 95% CIs = -10.77; -3.92), which is presented in Figure 6. In addition, sensitivity analysis showed that the results of this meta-analysis were credible (details in Supplementary Material, FS4).

3.4.5. Safety Evaluation. Only three trials reported the clinical adverse events among these studies, including dizziness, gastrointestinal discomfort, and high fever. Considering potential clinical and methodological heterogeneity, even  $l^2$  statistic (statistical heterogeneity) < 50%, the random effects model was used to perform the meta-analysis. The results of this meta-analysis showed that EA compared with no EA showed no significant difference (OR = 0.17, 95% CIs = 0.02; 1.49), which is presented in Figure 7. In addition, sensitivity analysis showed that the results were not credible (details in Supplementary Material, FS5).

*3.4.6. The Incidence of Postherpetic Neuralgia.* In our study, postherpetic neuralgia referred to pain in the lesion area after 1 month of herpes zoster. This result was in agreement



FIGURE 8: Funnel plot of the incidence of postherpetic neuralgia.



FIGURE 9: Meta-analysis results of publication bias.

with previous reports [27, 28]. Three trials reported the incidence of postherpetic neuralgia. Considering potential clinical and methodological heterogeneity, even  $I^2$  statistic (statistical heterogeneity) < 50%, the random effects model was used to perform the meta-analysis. The results of this meta-analysis showed that EA compared with no EA showed a significant difference (OR = 0.20, 95% CIs = 0.07; 0.55), which is presented in Figure 8. In addition, sensitivity analysis showed that the results were not credible (details in Supplementary Material, FS6).

3.5. Publication Bias. Publication bias is a potential concern in meta-analyses when interpreting the results. In this study, the funnel plot and Begg's tests were used to assess the publication bias. [29] Publication bias was indicated by an asymmetry funnel around the pooled effect size. Here, it was worthwhile to notice that those studies lay not symmetrically around the pooled effect size, and the Begg's tests also revealed statistically significant publication bias (p < 0.05); the result is presented in Figure 9.

#### 4. Discussion

Herpetic neuralgia is the most common and frequent clinical symptom after herpes zoster. Here, we launched a systematic review and meta-analysis to determine the efficacy and safety of EA for pain control in herpetic neuralgia patients. The present results indicated that EA was effective for pain control in herpetic neuralgia patients. Moreover, the time to rash healing and reducing the incidence of postherpetic neuralgia were remarkable. Nonetheless, only a minority of the studies have reported the adverse effect during the study; therefore, our study could not identify the safety of EA for pain control in herpetic neuralgia patients. Furthermore, only a small number of studies have reported the cessation of pustules and time to scabs in herpetic neuralgia patients; therefore, our meta-analysis could not determine the effectiveness of EA for the cessation of pustules and time to scabs. Overall, this is the first meta-analysis to conduct the study on efficacy and safety of EA for pain control in herpetic neuralgia patients. Hence, our study is very valuable; all details of this study are summarized below.

It is important to note that EA is effective for the treatment of acute pain in herpetic neuralgia patients. Previous studies suggest that EA is associated with reducing chronic pain, such as cervical myofascial pain syndrome and knee osteoarthritis. [12, 30] In addition, some studies indicate that EA is associated with reduced acute pain, including acute postoperative pain. [31] This study revealed that EA might also alleviate acute pain in herpetic neuralgia patients. Preclinical studies suggest that EA may lead to more substantial analgesic outcomes than manual acupuncture. [32] Moreover, it can decrease the risk of drug-drug interactions and the adverse effects of pharmaceutical drugs owing to their role in reducing the administration of analgesics. EA is defined as combining acupuncture and electric stimulation by inserting acupuncture into acupoints and passing a microcurrent close to human bioelectricity on the needle. [33] A previous study has shown that EA performed at different frequencies exhibits different analgesic effects. [12] In the present study, subgroup analysis found that 2/100 Hz-EA was better than 2 Hz-EA. The results obtained were consistent with the following studies: alternating low and high frequencies EA has a more potent analgesic effect than constant frequency EA. [34-36] In addition, for the acupoint of EA stimulation, the most commonly used points is Jiaji (EX-B2), followed by Zhigou (TE6), and Houxi (SI3). Jiaji (EX-B2) is located in the back region 0.5 inches lateral to the posterior median line. A previous study has shown that EA on Jiaji (EX-B2) can treat neuropathic pain. [37] Yet, as far as we know, no evidence for Zhigou (TE6) and Houxi (SI3) is observed.

It is also noteworthy that EA is effective for other symptoms and complications in herpetic neuralgia patients. First, the outcomes, indicator of skin lesions, including the rash healing time, pustules time, and scabs time, are commonly assessed in a clinical setting. In terms of the rash healing time, EA might also have a positive effect (MD = -7.35, 95% CIs = -10.77; -3.92). However, EA showed no positive effect in the cessation of pustules time and scabs time. Sensitivity analysis revealed that the metaanalysis result was not stable. Specifically, one study reported negative results [22], two studies reported positive results [21, 24]. The possible reason is that these outcomes mainly relied on the clinician's subjective judgment, which may easily lead to a detection bias. Due to this, more objective, precise, accurate, and reliable methods should be explored in daily clinical practice to identify skin lesions. In addition, this discrepancy may have been caused by the limited sample size. Second, in terms of the reduced incidence of postherpetic neuralgia, EA might have a positive effect (OR = 0.20, 95% CIs = 0.07; 0.55). It is generally known that postherpetic neuralgia is the most common intractable pain and seriously affects a patient's quality of life. In addition, it is very tricky to treat postherpetic neuralgia. Thus, effective prevention of postherpetic neuralgia is crucial for herpetic neuralgia patients. In our study, we found that EA might be a promising technique with a positive effect in the prevention of postherpetic neuralgia.

The safety of EA is also an important issue in herpetic neuralgia patients. Although EA can relieve acute pain in herpetic neuralgia patients and reduce the incidence of postherpetic neuralgia, we should also pay more attention to the safety aspects and adverse effects of EA. Regrettably, there is still a lack of evidence regarding the safety of EA in herpetic neuralgia patients. Only two of the six studies reported the adverse events, but the studies were underpowered to detect clinically significant differences in negative event rates. Several reasons for this are possible. First, the likely reason is that the sample size may be too small. Second, some researchers may believe that side effects were limited in severity and failed to report them. Although there are many studies with clear evidence of the safety of EA for treating pain [38], there is no convincing evidence concerning its safety in terms of EA for acute herpes zoster. Therefore, future studies should provide more details on the safety profile, regardless of favorable or unfavorable outcomes.

It is worth noting that the small sample sizes and poor methodological quality trials included in this review require attention. On the one hand, there were fewer studies, mostly with smaller sample sizes. In some trials, the sample size was as small as 12, and the largest trial had a sample size of 45. As a result, we detected potential publication bias cases using the observed funnel plot asymmetry. Therefore, to some extent, the small sample size limited the reliability of the estimated effects. On the other hand, there was remarkable heterogeneity between the studies regarding the intervention design. In particular, wide variation within the acupoints selected was observed. Since the efficacy of each acupoint may vary greatly, the pooled analysis results may not be generalizable to all included acupoint selection. In addition, EA as a procedural intervention was applied in the experimental group, and a similar procedural intervention was not conducted in the control group, the differences observed between the pooled experimental and control groups might

be at least partially addressed by the differences in the placebo effect of these interventions. In addition, the sessions and courses of EA were not the same.

4.1. Limitation. There are some deficiencies in this study that need to be addressed. First, the sample size of the studies included in this view was relatively small. It is wellknown that larger sample sizes may provide higher accuracy. Thus, we encourage authors to give the estimate sample size method using the statistical method. Second, the heterogeneity of study design of these studies was relatively high; for this reason, we encourage authors to register study protocols to improve the heterogeneity of experimental studies. Third, the methodological quality of these studies was relatively low. The lack of methodological quality among the included studies also limited the robustness of the results of this meta-analysis. Therefore, we encourage authors to precisely follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines.

### 5. Conclusion

Our results showed that EA could offer certain advantages in treating acute pain in herpetic neuralgia patients. However, small sample sizes, heterogeneity in study design, and variable methodological quality weaken these inferences. In addition, weak evidence was found for the safety of EA.

#### **Data Availability**

Data are available in a public, open access repository. All data relevant to the study are included within the article or uploaded as supplementary information.

#### **Ethical Approval**

This study presents an overview of existing published literature, and ethics approval is not required.

#### **Conflicts of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### **Authors' Contributions**

Kelin He and Fengjia Ni contributed equally to this work as co-first authors. Fengjia Ni and Yi Huang were involved in the literature inclusion and exclusion. Mengyi Zheng and Han Yu were involved in data collection. Dexiong Han participated in the later revision of the article. Ruijie Ma was involved in protocol design, draft preparation, and supervision. All authors critically revised the manuscript and approved its final version. Kelin He and Fengjia Ni contributed equally to this work.

#### Acknowledgments

This work was supported by the Zhejiang Province Program for the Cultivation of High-level Health Talents, the Young Top-notch Talent of Ten Thousand Plan in Zhejiang Province, the Chinese Medicine Research Program of Zhejiang Province (no. 2019ZB057).

#### **Supplementary Materials**

Supplementary materials of sensitivity analysis results are available at Evidence-Based Complementary and Alternative Medicine online. (*Supplementary Materials*)

#### References

- M. A. Nagel and D. Gilden, "Neurological complications of varicella zoster virus reactivation," *Current Opinion in Neurology*, vol. 27, no. 3, pp. 356–360, 2014.
- [2] W. Opstelten, J. McElhaney, B. Weinberger, A. L. Oaklander, and R. W. Johnson, "The impact of varicella zoster virus: chronic pain," *Journal of Clinical Virology*, vol. 48, pp. S8–S13, 2010.
- [3] K. M. O'Connor and D. S. Paauw, "Herpes zoster," *Medical Clinics of North America*, vol. 97, no. 4, pp. 503–522, 2013.
- [4] H. Bricout, M. Haugh, O. Olatunde, and R. G. Prieto, "Herpes zoster-associated mortality in Europe: a systematic review," *Bio Medical Central Public Health*, vol. 15, p. 466, 2015.
- [5] S. K. Tyring, "Management of herpes zoster and postherpetic neuralgia," *Journal of the American Academy of Dermatology*, vol. 57, pp. S136–S142, 2007.
- [6] E. Y. Gan, E. A. Tian, and H. L. Tey, "Management of herpes zoster and post-herpetic neuralgia," *American Journal of Clinical Dermatology*, vol. 14, no. 2, pp. 77–85, 2013.
- [7] Y. T. Chen, H. H. Wang, T. J. Wang, Y. C. Li, and T. J. Chen, "Early application of low-level laser may reduce the incidence of postherpetic neuralgia (PHN)," *Journal of the American Academy of Dermatology*, vol. 75, no. 3, pp. 572–577, 2016.
- [8] X. F. Xing, Z. F. Zhou, F. J. Zhang, and M. Yan, "The effect of early use of supplemental therapy on preventing postherpetic neuralgia: a systematic review and meta-analysis," *Pain Physician*, vol. 20, no. 6, pp. 471–486, 2017.
- [9] A. J. Vickers, E. A. Vertosick, G. Lewith et al., "Acupuncture for chronic pain: update of an individual patient data metaanalysis," *The Journal of Pain*, vol. 19, no. 5, pp. 455–474, 2018.
- [10] R. B. Kelly and J. Willis, "Acupuncture for pain," American Family Physician, vol. 100, no. 2, pp. 89–96, 2019.
- [11] S. Y. Seo, K. B. Lee, J. S. Shin et al., "Effectiveness of acupuncture and electroacupuncture for chronic neck pain: a systematic review and meta-analysis," *American Journal of Chinese Medicine*, vol. 45, no. 8, pp. 1573–1595, 2017.
- [12] Z. T. Lv, L. L. Shen, and B. Zhu, "Effects of intensity of electroacupuncture on chronic pain in patients with knee osteoarthritis: a randomized controlled trial," *Arthritis Re*search and Therapy, vol. 21, no. 1, p. 120, 2019.
- [13] S. Park, Y. R. Lyu, S. J. Park, M. S. Oh, I. C. Jung, and E. J. Lee, "Electroacupuncture for post-thoracotomy pain: a systematic review and meta-analysis," *PLoS One*, vol. 16, no. 7, Article ID e0254093, 2021.
- [14] R. Zhang, L. Lao, K. Ren, and B. M. Berman, "Mechanisms of acupuncture-electroacupuncture on persistent pain," *Anesthesiology*, vol. 120, no. 2, pp. 482–503, 2014.

- [15] H. P. Li, W. Su, Y. Shu et al., "Electroacupuncture decreases Netrin-1-induced myelinated afferent fiber sprouting and neuropathic pain through μ-opioid receptors," *Journal of Pain Research*, vol. 12, pp. 1259–1268, 2019.
- [16] C. H. Wu, Z. T. Lv, Y. Zhao et al., "Electroacupuncture improves thermal and mechanical sensitivities in a rat model of postherpetic neuralgia," *Molecular Pain*, vol. 9, p. 18, 2013.
- [17] D. Moher, L. Shamseer, M. Clarke et al., "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement," *Systematic Reviews*, vol. 4, no. 1, p. 1, 2015.
- [18] J. P. Higgins, D. G. Altman, and P. C. Gøtzsche, "The cochrane collaboration's tool for assessing risk of bias in randomised trials," *British medical Journal*, vol. 343, Article ID d5928, 2011.
- [19] M. Borenstein, L. V. Hedges, J. P. Higgins, and H. R. Rothstein, "A basic introduction to fixed-effect and random-effects models for meta-analysis," *Research Synthesis Methods*, vol. 1, no. 2, pp. 97–111, 2010.
- [20] J. J. Shuster, "Review: cochrane handbook for systematic reviews for interventions, version 5.1.0 published 3/2011. julian p.t. higgins and sally green, editors," *Research Synthesis Methods*, vol. 2, no. 2, pp. 126–130, 2011.
- [21] Y. N. Song, The Study of the Clinical Effect of Treating Acute Herpes Zoster with Electroacupuncture, Guangzhou University of Chinese Medicine, Guangzhou, China, 2009.
- [22] L. X. Li, C. Y. Chen, G. H. Lin, Y. Liu, Q. Li, and T. T. Zhao, "Clinical observation of electroacupuncture in treating 27 cases of acute herpes zoster," *Journal of New Chinese Medicine*, vol. 43, pp. 103–105, 2011.
- [23] P. C. Lin, Clinical Research on Electric Acupuncture Therapy in the Treatment of Acute Neuralgia Associated with Herpes Zoster, Guangzhou University of Chinese Medicine, Guangzhou, China, 2015.
- [24] X. P. Lu, "Clinical research of electroacupuncture in treating 13 cases of acute herpes zoster," *Inner Mongolia Traditional Chinese Medicine*, vol. 36, no. 8, p. 121, 2017.
- [25] R. Wei, "Clinical research on electroacupuncture in the treatment of acute neuralgia associated with herpes zoster," *World Latest Medicine Information*, vol. 19, no. 76, p. 201, 2019.
- [26] L. Cheng, Electro Acupuncture at Jiaji Point for Analgesic Effect of Herpes Zoster and its Influence on Serum C3, C4, Hubei University of Chinese Medicine, Wuhan, China, 2018.
- [27] R. van Seventer, A. Sadosky, M. Lucero, and E. Dukes, "A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia," *Age and Ageing*, vol. 35, no. 2, pp. 132–137, 2006.
- [28] Y. Huang, C. Xu, T. Zeng et al., J. Li, T. Huang, H. Huai et al., Intravenous patient-controlled analgesia hydromorphone combined with pregabalin for the treatment of postherpetic neuralgia: a multicenter, randomized controlled study," *Korean Journal of Pain*, vol. 34, no. 2, pp. 210–216, 2021.
- [29] C. B. Begg and M. Mazumdar, "Operating characteristics of a rank correlation test for publication bias," *Biometrics*, vol. 50, no. 4, pp. 1088–1101, 1994.
- [30] F. Eslamian, F. Jahanjoo, N. Dolatkhah, A. Pishgahi, and A. Pirani, "Relative effectiveness of electroacupuncture and biofeedback in the treatment of neck and upper back myofascial pain: a randomized clinical trial," *Archives of Physical Medicine and Rehabilitation*, vol. 101, no. 5, pp. 770–780, 2020.
- [31] L. X. An, X. Chen, X. J. Ren, and H. F. Wu, "Electro-acupuncture decreases postoperative pain and improves recovery

in patients undergoing a supratentorial craniotomy," *American Journal of Chinese Medicine*, vol. 42, no. 5, pp. 1099–1109, 2015.

- [32] H. M. Langevin, R. Schnyer, H. MacPherson et al., "Manual and electrical needle stimulation in acupuncture research: pitfalls and challenges of heterogeneity," *Journal of Alternative and Complementary Medicine*, vol. 21, no. 3, pp. 113–128, 2015.
- [33] J. Comachio, M. Oliveira Magalhães, T. Nogueira Burke et al., "Efficacy of acupuncture and electroacupuncture in patients with nonspecific low back pain: study protocol for a randomized controlled trial," *Trials*, vol. 16, p. 469, 2015.
- [34] J. S. Han, "Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies," *Trends in Neurosciences*, vol. 26, no. 1, pp. 17–22, 2003.
- [35] C. Niu, H. Hao, J. Lu, L. Li, Z. Han, and Y. Tu, "A novel uniacupoint electroacupuncture stimulation method for pain relief," *Evidence Based Complement Alternative Medicine*, vol. 2011, Article ID 209879, 6 pages, 2011.
- [36] J. R. da Silva, M. L. da Silva, and W. A. Prado, "Electroacupuncture at 2/100 hz activates antinociceptive spinal mechanisms different from those activated by electroacupuncture at 2 and 100 hz in responder rats," *Evidence Based Complement Alternative Medicine*, vol. 2013, Article ID 205316, 14 pages, 2013.
- [37] Z. Z. Ma, Y. C. Lu, J. J. Wu, X. X. Xing, X. Y. Hua, and J. G. Xu, "Acupuncture induces reduction in limbic-cortical feedback of a neuralgia rat model: a dynamic causal modeling study," *Neural Plasticity*, vol. 2020, Article ID 5052840, 11 pages, 2020.
- [38] J. Wu, B. Chen, X. Yin, P. Yin, L. Lao, and S. Xu, "Effect of acupuncture on post-hemorrhoidectomy pain: a randomized controlled trial," *Journal of Pain Research*, vol. 11, pp. 1489– 1496, 2018.