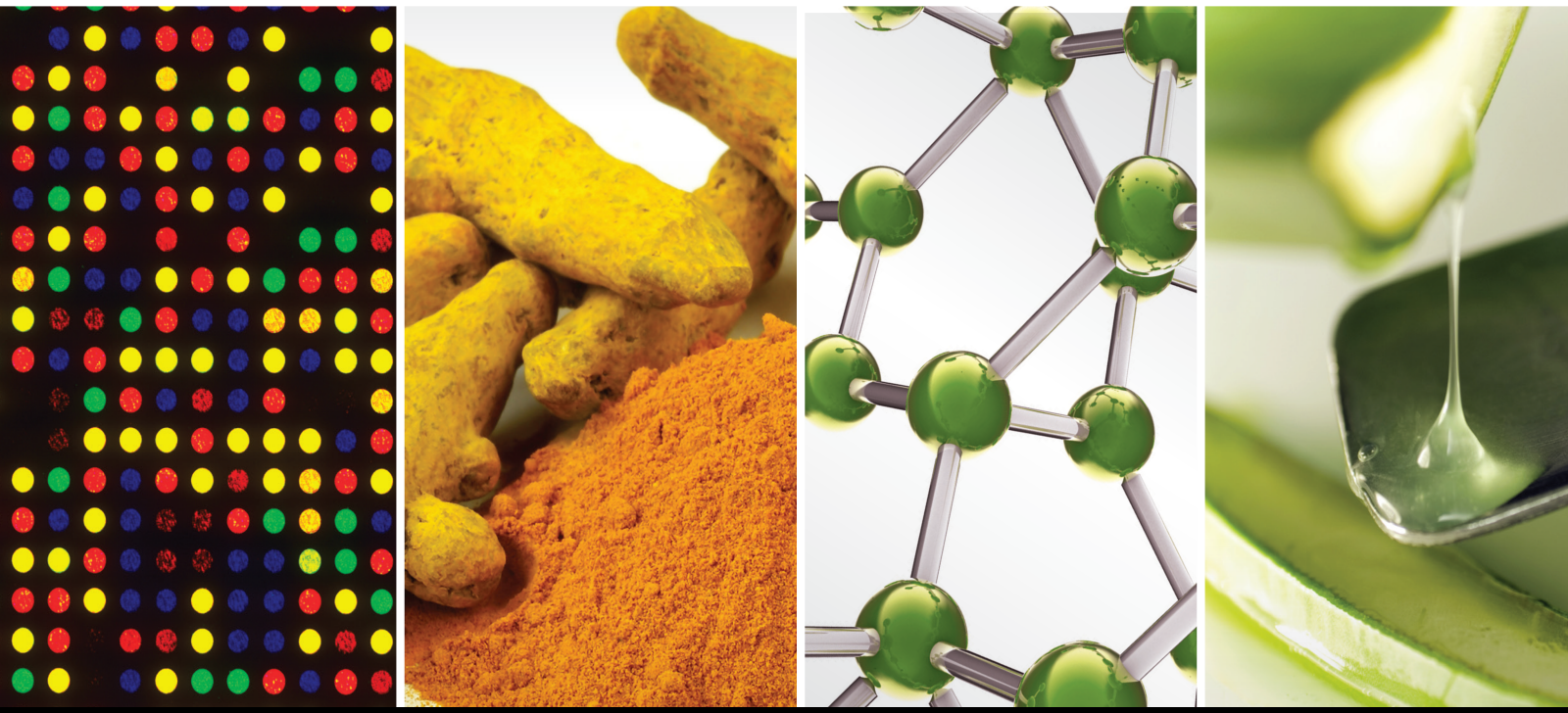
Evidence-Based Complementary and Alternative Medicine

Current Trends in Research of Acupuncture Analgesia

Lead Guest Editor: Yi-Hung Chen
Guest Editors: Younbyoung Chae and Cheng-Hao Tu



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Research Article

Electroacupuncture Alleviates Diabetic Neuropathic Pain and Downregulates p-PKC and TRPV1 in Dorsal Root Ganglions and Spinal Cord Dorsal Horn

Yi-qi Ma, Qun-qi Hu, Yu rong Kang, Li-qian Ma, Si-ying Qu, Han-zhi Wang, Yin-mu Zheng, Si-yi Li, Xiao-mei Shao, Xiao-yu Li, Han-tong Hu, Yong-liang Jiang, Jian-qiao Fang, and Xiao-fen He

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Diabetic neuropathic pain (DNP) is a common complication of diabetes. Streptozotocin (STZ)-induced changes of protein in dorsal root ganglion (DRG) and spinal cord dorsal horn (SCDH) are critical for DNP genesis. However, which proteins change remains elusive. Here, the DNP model was established by a single intraperitoneal injection of STZ, accompanied by increased fasting blood glucose (FBG), decreased body weight (BW), and decreased paw withdrawal latency (PWL). Proteins change in L4-L6 DRGs and SCDH of rats were detected. Western blot and immunofluorescence results showed that expression levels of phosphorylated protein kinase C (p-PKC), transient receptor potential vanilloid-1 (TRPV1), Substance P (SP) and calcitonin gene-related peptide (CGRP) in the DRG and the SCDH of rats were increased after STZ injection. A preliminary study from our previous study showed that 2 Hz electroacupuncture (EA) effectively alleviates DNP. However, the analgesic mechanism of EA needs further elucidation. Here, EA at the bilateral Zusanli (ST36) and KunLun (BL60) acupoints was applied for one week, and to investigate the effect on DNP. EA reversed thermal hyperalgesia in DNP rats and downregulated the expression of p-PKC, TRPV1, SP, and CGRP in DRG and SCDH.

1. Introduction

Diabetes is a common metabolic disease [1], and the incidence of diabetes is on the rise [2]. Hyperglycemia can induce metabolic, microvascular lesions, and cause various acute and chronic neuropathy conditions [3]. Diabetic neuropathic pain (DNP) is a major complication of diabetes [4–6], which is mainly characterized by spontaneous pain, paresthesia and hyperalgesia, leading to a decrease in the quality of life of patients [7–9]. The mechanisms underlying DNP still remain unclear, and need further elucidation to produce the effectiveness of some conventional treatment options for DNP.

Dorsal root ganglion (DRG) neurons are the primary afferent nerve cells for trunk and extremity nociception. DRGs are implicated in transmitting and accommodating sensations and receiving and communicating nociception, and they play an important role in the mechanism of pain. Pain signals are transmitted from DRGs to the spinal cord dorsal horn (SCDH) [10, 11]. Neurons in the central processes of the horn and neurons in the DRG form the primary synapse, in which SCDH plays a role in relaying and processing sensory information. Therefore, DRGs and SCDH are key sites for studying neuropathic pain mechanisms. Previous studies report that several DRG pain-related ion channels, receptors and neuropeptides such as Ca^{2+} channels, Na^{+} channels, phosphorylated protein kinase C (p-PKC), transient receptor potential vanilloid-1 (TRPV1) [12], calcitonin gene-related peptide (CGRP), and substance P

(SP) [13] are implicated in the transmission of pain. Preliminary studies indicate that p-PKC, TRPV1, SP, and CGRP in DRG play fundamental roles in acute neurogenic inflammation [12]. However, the changes in p-PKC, TRPV1, SP, and CGRP expression in DRG and SCDH in DNP model have not been systematically studied.

Although clinical drugs are used to alleviate DNP, clinical studies have failed to prove the effectiveness of treatment with less adverse effects [14, 15]. Electroacupuncture (EA) therapy is an effective option for chronic pain, including DNP treatment [16], which combines electrical stimulation with the use of acupuncture needles [17–19]. Our previous study showed that 2 Hz EA was more effective than 100 Hz EA in relieving DNP [20]. However, the precise mechanism of 2 Hz EA on DNP has not been fully elucidated.

The present study sought to explore the effect of STZ administration on expressions of p-PKC, TRPV1, SP, and CGRP in DRG and SCDH. These findings will provide a basis for understanding the mechanism of DNP. Moreover, the effect of 2 Hz EA treatment on the expression levels of p-PKC, TRPV1, SP, and CGRP in DRGs and SCDH of DNP rats was explored.

2. Materials and Methods

2.1. Animals. Male Sprague-Dawley rats (180 ± 20 g) were used in the present study. Rats were assigned to five groups and lived in separate cages. Animals had free access to food and water. Rats were maintained in a controlled environment (20–24°C and 40–60%) with 12-h light/dark cycles at the Animal Laboratory Center of Zhejiang Chinese Medical University (SYXK (zhe) 2018-0012). Experiments were conducted after acclimatization of animals for a week. All experimental procedures were conducted according to animal management regulations. The Animal Welfare Committee of Zhejiang Chinese Medical University approved all protocols in the present study (IACUC-20190805-04).

2.2. Establishment of the DNP Rat Model. Rats were fasted for 16 hours and STZ (65 mg/kg, S0130, Sigma) dissolved in sodium citrate buffer (0.1 mol/L, pH 4.5) was administered into rats intraperitoneally [21, 22]. Rats in the Control group received the same volume of the vehicle. Fasting blood glucose (FBG) was determined 3 days after STZ injection. Rats with FBG >13.9 mmol/L [23, 24] and thermal nociceptive sensitivity were used as the criteria for a DNP rat model. Animals that met these criteria were used in subsequent experiments.

2.3. Experimental Procedures. The experiment was split into two phases. The effect of STZ on inducing diabetic neuropathic pain was evaluated in the first phase. Rats were randomly assigned to two groups: (1) Control group ($n = 10$, all rats were sacrificed and tissues were harvested after 3 weeks of experiment); (2) STZ group ($n = 30$, 10 rats were killed and tissues were harvested after 1 week, 2 weeks and 3 weeks of experiment). Expression levels of p-PKC, TRPV1, SP, and CGRP in lumbar 4–6 SCDH and DRGs were determined by western blot (WB) or immunofluorescence (IF) analysis. In the second phase, the analgesic effect of EA on DNP and whether p-PKC, TRPV1, SP, and CGRP are implicated in this effect was explored. Rats were randomly assigned to three groups ($n = 8$): (1) Control group; (2) STZ group; and (3) STZ + EA group. Rats in the STZ + EA group were administered with EA daily for a week from the 2 weeks. Tissues were harvested after treatment for western blot and immunofluorescence analysis. Expression levels of p-PKC, TRPV1, SP, and CGRP in lumbar 4–6 SCDH and DRGs were determined by WB or IF.

2.4. Determination of Fasting Blood Glucose and Body Weight. Rats were fasted for 8 h and weighed. Blood was obtained from the tail and analysis of FBG was performed using ACCU-CHEK Performa blood glucose meter (Roche Diagnostics GmbH, Germany) a day before administration of STZ and 1 week, 2 weeks, and 3 weeks after STZ injection.

2.5. Assessment of Thermal Hypersensitivity. Paw withdrawal latency (PWL) analysis was conducted using the plantar test (37370, Ugo Basile, Italy). Rats were acclimatized in the Plexiglas cubicles (11.5 cm × 17 cm × 14 cm) on the glass plate for at least 30 min, before evaluation. The cut-off time was set at 30 s, and the radiant heat was set to 40, to avoid damage of rat tissue. The light beam was turned off and the timing stopped when the rat raised its paw. The experiment was conducted 3 times per rat with an interval of 5 min between replicates. PWL was calculated as the average of the latencies in seconds.

2.6. EA Treatment. Rats in STZ + EA group received EA treatment once a day for one week. Rats that received EA were not anesthetized, but immobilized gently with a self-made retainer. The selected acupoints were bilateral Zusanli (ST36, 5 mm below the fibular head and 1 mm outside the anterior tibial edge) and Kunlun (BL60, depression between the lateral ankle joint and achilles tendon of the hind limb) points. The acupuncture needles (0.25 mm × 13 mm, Hua Tuo, Suzhou Medical Appliance Factory, Jiangsu Province) were carefully inserted into the acupuncture points, and then the acupuncture needles were inserted at a depth of 3 mm for the Kunlun point and 7 mm for the Zusanli point, and then connected to the HANS acupoint electrical stimulation device (Hans-200A, Jisheng Medical Technology, Beijing, China) for 30 minutes. The HANS acupoint electrical stimulation device was set at 1 mA and 2 Hz. Rats in the other groups underwent the same sedation process without EA stimulation.

2.7. Western Blot. Experimental rats were anesthetized with sodium pentobarbital (80 mg/kg, i.p), then SCDH and L4-L6 DRGs were harvested. The tissues were homogenized in RIPA Lysis Buffer (P0013B, Beyotime, China) containing a mixture of protease inhibitors (P1050, Beyotime, China) and phosphatase inhibitors (P1050, Beyotime, China) and then

centrifuged at 12000 × rpm at 4°C for 20 min. The supernatant was used to identify protein concentration using BCA Protein Assay Kits (23225, Thermo Fisher, USA). The supernatant was diluted with 2 × loading buffer solution and boiled at 100°C for 3 min. Equal amounts of proteins (20 μg) were separated using SDS-PAGE gels electrophoresis and transferred to polyvinylidene difluoride membranes. Subsequently, the membranes were incubated in 5% nonfat milk diluted with 1 × TBST (pH 7.5) for 1 h. Further, the membranes were incubated with rabbit anti-phospho-PKC (1 : 1000; AF3197, Affinity, USA), rabbit anti-TRPV1 (1 : 1000; ACC030, Alomone, USA), and β-actin (1 : 5000; #12262, Cell Signaling Technology, USA) overnight at 4°C. Membranes were washed three times with 1 × TBST, 10 min and incubated with HRP-linked antibody (1 : 5000; #7074, Cell Signaling Technology, USA) for 2 h at room temperature. The membranes were then visualized by chemiluminescence (ECL Plus; Beyotime, China), and proteins bands were quantified using the Image Quant LAS 4000 system. Target protein levels were normalized against β-actin expression levels.

2.8. Immunofluorescence Analysis. Rats were anesthetized with sodium pentobarbital (80 mg/kg, i.p) and transcardially perfused with 4°C saline followed by 4% paraformaldehyde. The spinal cord and DRGs from L4 to L6 were harvested, postfixed in 4% paraformaldehyde for 4 h, and then dehydrated in 15% sucrose solution for 24 h and 30% for 48 h. Tissue sections were prepared using a frozen microtome (30 μm thickness for the spinal cord and 10 μm thickness for DRGs) and subsequently fixed onto glass slides. Sections were rinsed thrice with 1 × TBST for 10 min for each rinse, then blocked with 10% donkey serum for 1 h at 37°C. Sections were incubated with diluted guinea pig anti-TRPV1 (1 : 200; ACC-030-GP, Alomone, Israel) antibodies mixed with rabbit anti-SP (1 : 1500; ab67006, Abcam, UK) or rabbit anti-CGRP (1 : 800; #14959, Cell Signaling Technology) antibodies overnight at 4°C. Tissues slices were washed 6 times in 1 × TBST, for 10 min per wash, then incubated with Goat Anti-Guinea pig IgG H&L (ALexa Fluor® 488) (1 : 600; ab150185, Abcam, UK) and Goat Anti-Rabbit IgG H&L (Alexa Fluor® 594) (1 : 800; ab150084, Abcam, UK) for 1 h at 37°C. Tissue sections were sealed with antifade solution. The sections were then imaged under an Imager M2 microscope (ZEISS, Germany). The scale bar for SCDH slices was 100 μm and the objective magnification was 10×. The scale bar for DRG slices was 50 μm and the objective magnification was 20×. The mean fluorescence intensity of SP and CGRP in SCDH was determined by Image J and the number of SP, CGRP, and TRPV1 positive cells in DRGs was evaluated. Three sections were selected for each rat and three rats were analyzed for each group.

2.9. Statistical Analysis. Statistical analysis was conducted using SPSS 22.0 software. Data were presented as mean ± standard error of the mean (SEM). Independent *t*-test was carried out to compare two groups and one-way ANOVA followed by LSD or Dunnett's post hoc tests were used for the comparison of three or more groups. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Thermal Hyperalgesia in a Rat Model of STZ-Induced Diabetes. The experimental design for the first phase is given in Figure 1(a). The FBG in the STZ group was higher than the Control group on 1, 2, and 3 weeks (Figure 1(b), $P < 0.01$, respectively). The BW in the STZ group was lower than the Control group on 1, 2, and 3 weeks (Figure 1(c), $P < 0.01$, respectively). The PWL in the STZ group was lower than the Control group on 2 and 3 weeks (Figure 1(d), $P < 0.01$, respectively). These results revealed that the DNP model was successfully established on day 14 after STZ injection.

3.2. p-PKC, TRPV1, SP, and CGRP are Increased in the DRG after STZ Injection. To investigate the effect of STZ injection on the expression of p-PKC, TRPV1, SP, and CGRP in the L4-L6 DRGs, we used WB and IF to measure those protein levels. WB results showed that STZ injection significantly increased the expressions of p-PKC, TRPV1, SP, and CGRP in the L4-L6 DRGs on 1 W, 2 W, and 3 W (Figure 2(c), $P < 0.05$, $P < 0.05$, $P < 0.05$; Figure 2(d), $P < 0.01$, $P < 0.01$, $P < 0.05$). Double immunofluorescence assays were performed to explore whether SP/TRPV1 and CGRP/TRPV1 were coexpressed in DRG cells (Figure 3). SP is a peptide mainly secreted by neurons and is involved in neurotransmission during injuries [25]. Moreover, CGRP is implicated in the transmission of pain signals [26]. The findings showed that CGRP was coexpressed with TRPV1 in DRG cells (Figure 3(a)), and SP was coexpressed with TRPV1 in DRG cells (Figure 3(b)). In addition, positive cell counts showed that the number of TRPV1-positive, CGRP-positive in DRG was increased significantly starting 1 week after STZ injection (Figure 3(c), $P < 0.01$, $P < 0.01$, $P < 0.01$; Figure 3(d), $P < 0.05$, $P < 0.01$, $P < 0.01$). SP-positive, TRPV1/CGRP-positive, and TRPV1/SP-positive cells in DRG were significantly increased starting 2 week after STZ injection (Figure 3(e), $P < 0.01$, $P < 0.01$, Figure 3(f), $P < 0.01$, $P < 0.01$ Figure 3(h), $P < 0.01$, $P < 0.01$). Venn diagram showed that the number of coexpressing cells in the DRG of the 3 W group was significantly increased compared to Control group (Figures 3(g) and 3(i)).

3.3. p-PKC, TRPV1, SP, and CGRP are Increased in the SCDH after STZ Injection. The expression levels p-PKC, TRPV1, SP, and CGRP in SCDH were determined to explore the effect of STZ on SCDH (Figures 4 and 5). WB results indicated that the p-PKC protein was increased from one to three weeks (Figure 4(c), $P < 0.01$, $P < 0.01$, $P < 0.01$), and TRPV1 protein was increased from two to three weeks (Figure 4(d), $P < 0.05$, $P < 0.01$). IF results showed SP and CGRP increased from one to three weeks (Figures 4(g) and 4(h), $P < 0.01$, respectively). Moreover, IF results demonstrated the coexpression of SP/TRPV1 and CGRP/TRPV1 in the SCDH (Figures 5(a) and 5(b)).

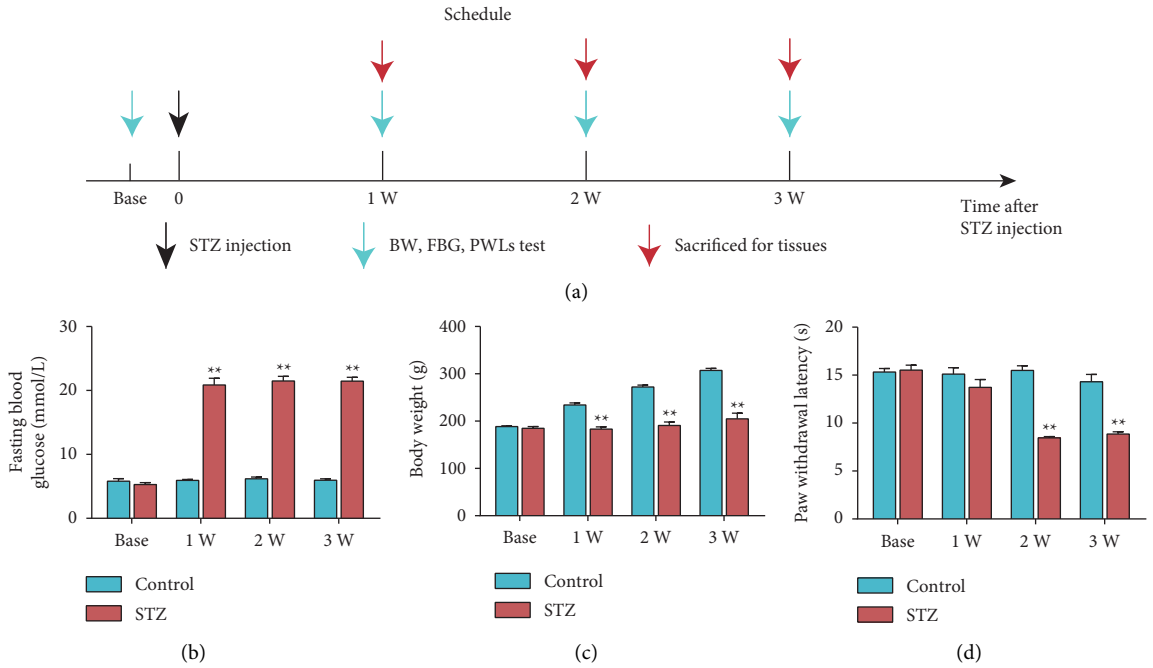


Figure 1: Establishment of DNP rat model by STZ administration. (a) Procedure for generating the DNP rat model. Time course effect of STZ on FBG (b), BW (c), and PWL (d). Data are presented as mean ± SEM, $n = 10$ per group. $^{**}P < 0.01$ vs. Control group.

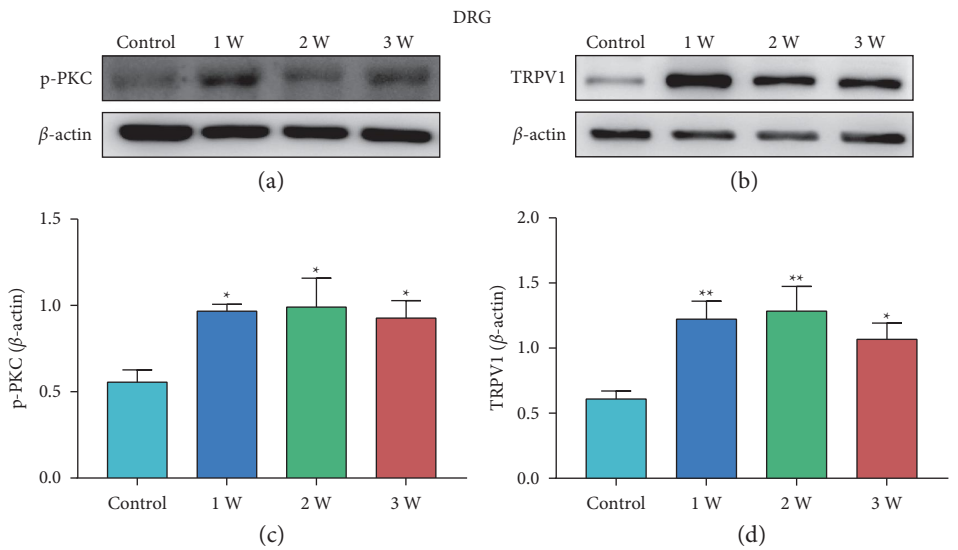
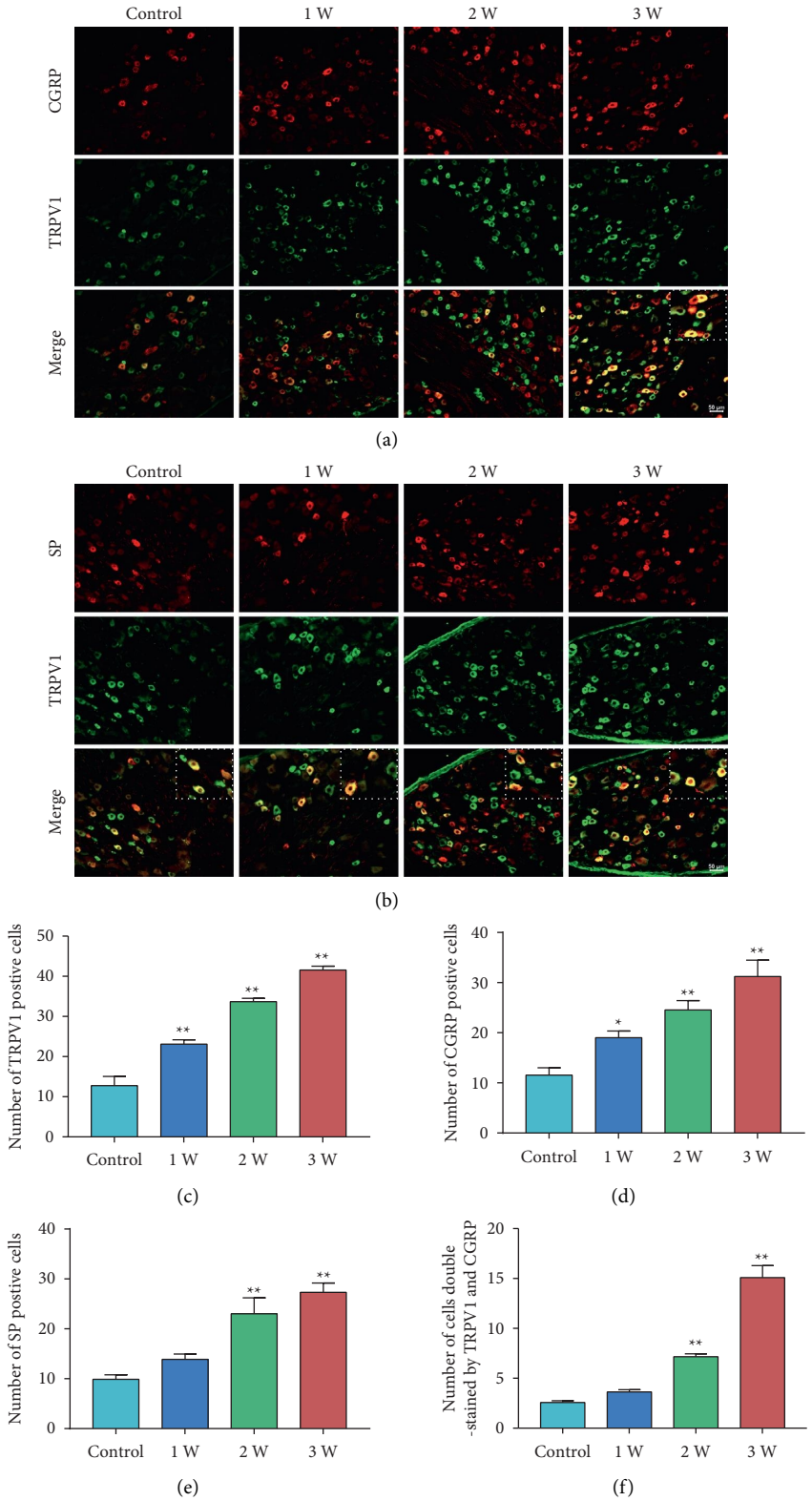


Figure 2: Protein expression of p-PKC and TRPV1 in DRG of rats in STZ group. (a, b) Representative images of WB result of p-PKC and TRPV1 in DRG from different groups. (c, d) WB showed the increased p-PKC and TRPV1 expression in DRG in STZ group rats compared to control rats. Data are presented as mean ± SEM, $n = 5$ per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control group.

3.4. EA Alleviates Thermal Hyperalgesia in a Rat Model of STZ-Induced DNP. The experimental design is given in Figure 6(a). The FBG in the STZ group was increased, and the BW in the STZ group was decreased at 1, 2, and 3 weeks (Figures 6(b) and 6(c), $P < 0.01$, respectively). The PWL in the STZ group decreased at 2 and 3 weeks, indicating the successful establishment of DNP in rats (Figure 6(d), $P < 0.01$, respectively). The rats in the STZ + EA group were treated with EA from the 15th day to the 21st day. EA reduced STZ-induced thermal hyperalgesia in DNP rat models in the third week (Figure 6(d), $P < 0.01$). However, EA did not produce an effect on FBG and BW in DNP rats in the third week (Figures 6(b) and 6(c), $P > 0.05$, respectively).

3.5. EA Reduces Expression of p-PKC, TRPV1, SP, and CGRP in the DRG of DNP Rats. Further WB and IF analyses were conducted to explore the effect of EA treatment on p-PKC, TRPV1, SP, and CGRP expression levels in L4-L6 DRGs of DNP rats (Figure 7). WB analysis showed p-PKC and



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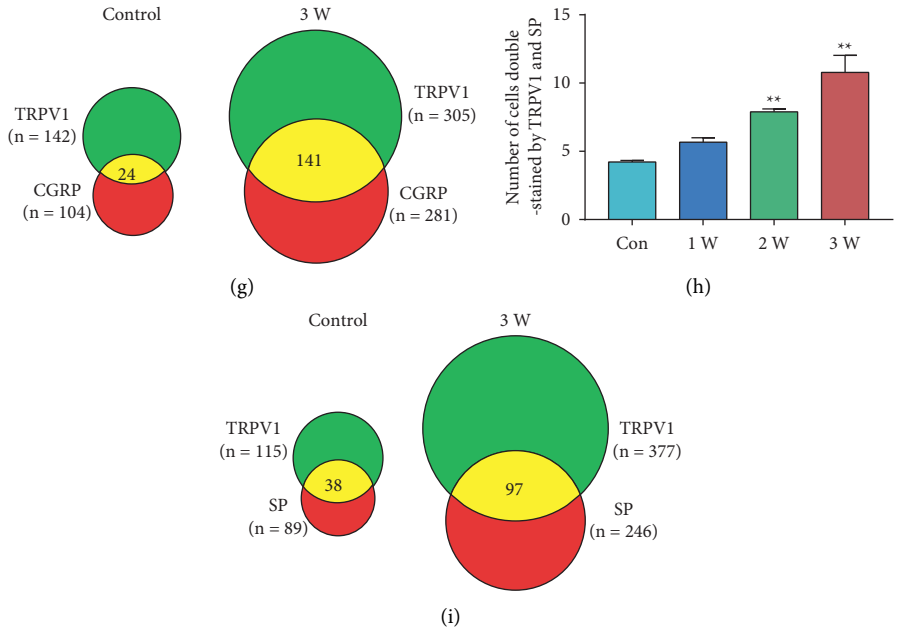

Figure 3: IF results of TRPV1, SP, and CGRP in DRG of rats in STZ group. (a) Representative images of IF of CGRP (red) and TRPV1 (green) in the DRGs from different groups. Scale bar: 50 μm. (b) Representative images of IF of SP (red) and TRPV1 (green) in DRG from different groups. Scale bar: 50 μm. (c) Number of TRPV1 positive cells in DRG from different groups. (d) Number of CGRP positive cells in DRG from different groups. (e) Number of SP positive cells in DRG from different groups. (f) Number of cells double stained by TRPV1 and CGRP in DRG from different groups. (g) The Venn diagram shows the number of neurons double-stained by TRPV1 and CGRP in L4-L6 DRGs, $n = 3$ rats. (h) Number of cells double stained by TRPV1 and SP in DRG from different groups. (i) The Venn diagram shows the number of neurons double-stained by TRPV1 and SP in L4-L6 DRGs. $n = 3$ rats. Data are presented as mean ± SEM, $n = 3$ per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control group.

TRPV1 expression in L4-L6 DRGs increased remarkably, compared to that of the Control rats (Figures 7(c) and 7(d), $P < 0.01$). EA treatment downregulated p-PKC and TRPV1 expression (Figures 7(c) and 7(d), $P < 0.01$). IF analysis showed that the numbers of TRPV1-positive, CGRP-positive, SP-positive, TRPV1/CGRP-positive, and TRPV1/SP-positive cells in DRG were significantly upregulated (Figures 8(c)–8(f) and 8(h), $P < 0.01$, $P < 0.05$, $P < 0.01$, $P < 0.01$, $P < 0.01$). EA treatment remarkably attenuated the upregulated number of those positively cells (Figures 8(c)–8(f) and 8(h), $P < 0.01$, $P < 0.05$, $P < 0.01$, $P < 0.01$, $P < 0.01$). The Venn diagram showed that the number of coexpressing cells in the DRG of the STZ + EA group was significantly lower than that of the STZ group (Figures 8(g) and 8(i)).

3.6. EA Reduces Expression of p-PKC, TRPV1, SP, and CGRP in the SCDH of DNP Rats. Further WB and IF analyses were conducted to explore expression levels of p-PKC, TRPV1, SP, and CGRP in SCDH of DNP rats after EA treatment (Figure 9). WB results indicated that p-PKC and TRPV1 expression increased remarkably. EA treatment decreased the increased expressions of p-PKC and TRPV1 (Figure 9(c), $P < 0.01$, $P < 0.05$; Figure 9(d), $P < 0.01$, $P < 0.01$). IF results indicated that STZ injection significantly increased the mean intensity of SP and CGRP in L4-6 SCDH (Figures 9(g) and 9(h), $P < 0.01$). Notably, EA stimulation remarkably reduced the mean intensity of SP and CGRP in L4-6 SCDH (Figure 9(g), $P < 0.01$; Figure 9(h), $P < 0.05$).

4. Discussion

In the current study, we investigated the changes of p-PKC, TRPV1, SP, and CGRP protein in DRG and SCDH in STZ-induced neuropathic pain. The results showed that the expressions of p-PKC, TRPV1, SP, and CGRP were increased in L4-6 DRG and SCDH, and TRPV1 was coexpressed with SP, and TRPV1 was also coexpressed with CGRP. We then examined the effect of 2 Hz EA on the thermal hyperalgesia of DNP model rats. In total, 2 Hz frequency of EA was applied for 30 minutes every day after DNP model establishment, from days 15 to 21. Results indicated that 2 Hz EA produced antiallodynic effect on DNP model rats, and EA effectively reduced overexpression of the p-PKC, TRPV1, SP, and CGRP marker proteins.

STZ is a glucosamine-nitrosourea that can selectively destroy pancreatic islet β-cells in mammals [27] and is commonly used in establishing diabetes models [28]. In this study, FBG increased and BW decreased remarkably starting at 1 week after STZ injection. PWL decreased remarkably starting at 2 weeks after STZ injection, indicating the successful establishment of the DNP model, which consisted with our previous research [29].

DRGs and SCDH play vital roles in many neuropathic pain [30–32]. DRG receives pain signals and transmits them

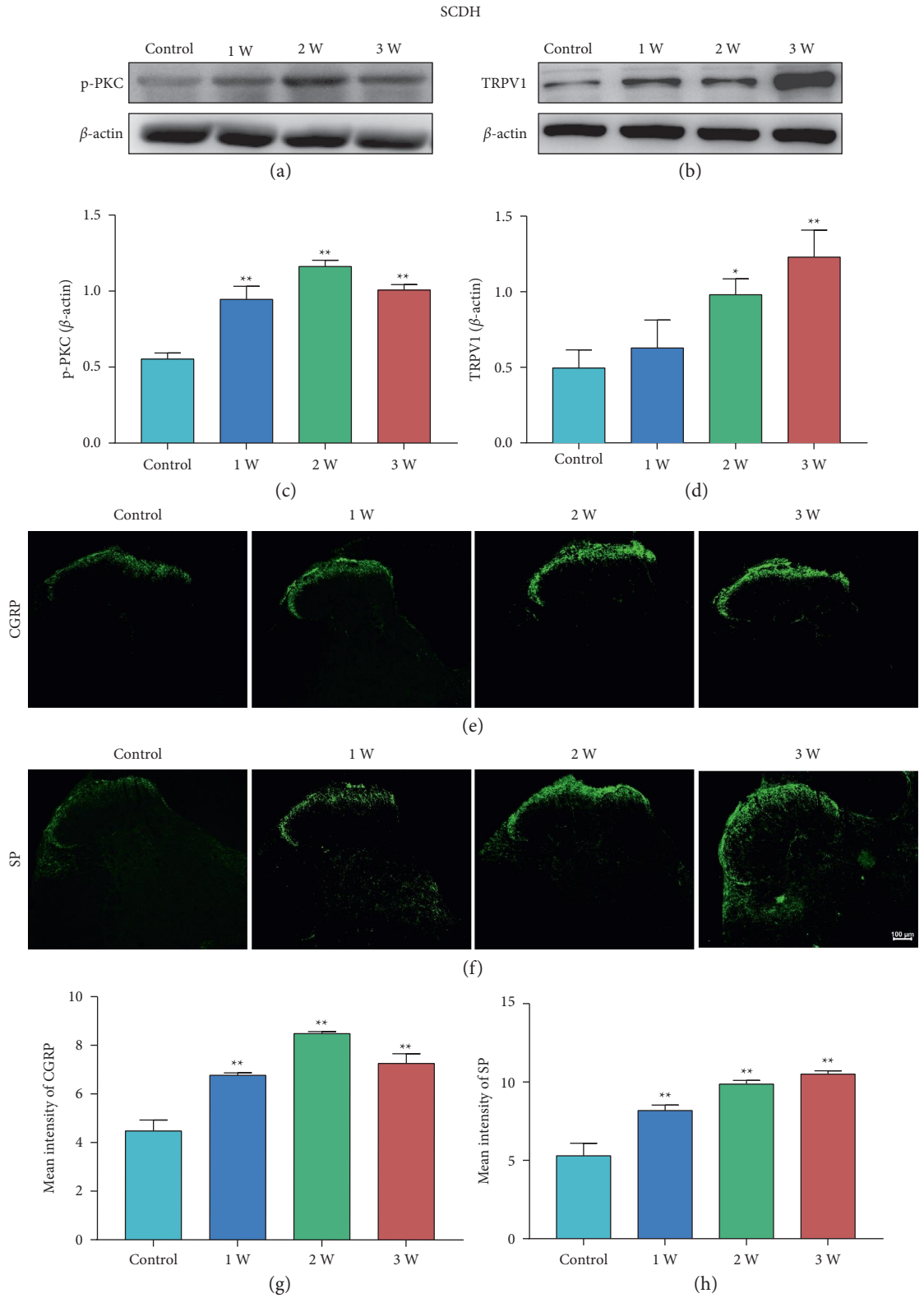

Figure 4: Protein expression of p-PKC and TRPV1 in SCDH of rats in STZ group. (a, b) Representative images of WB result of p-PKC and TRPV1 in SCDH from different groups. (c, d) WB showed the increased p-PKC and TRPV1 expression in SCDH in STZ group rats compared to Control rats. Data are presented as mean ± SEM, $n = 5$ per group. (e) Representative images of CGRP staining in SCDH. (f) Representative images of SP staining in SCDH. (g) Mean intensity analysis of CGRP staining in SCDH. (h) Mean intensity analysis of SP staining in SCDH. Scale bars=100 μm. Data are presented as mean ± SEM, $n = 3$ per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control group.

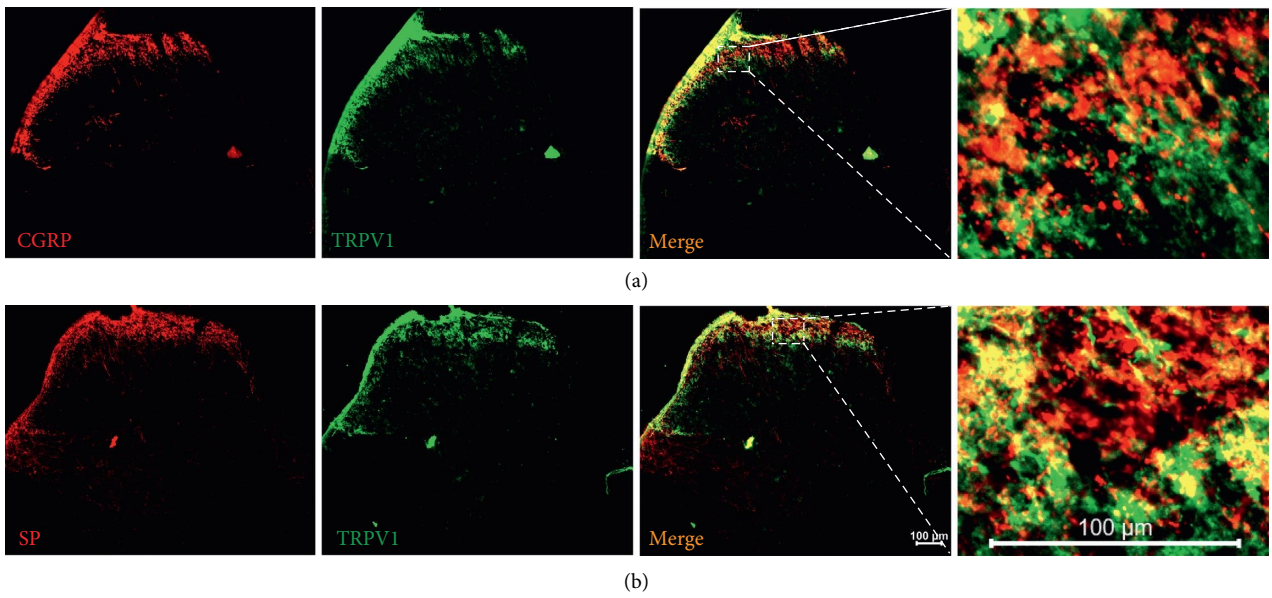

Figure 5: (a) Representative images of IF of CGRP/TRPV1 coexpression in SCDH. (b) Representative images of IF of SP/TRPV1 coexpression in SCDH Scale bars=100 μm. Data are presented as mean ± SEM, $n = 3$ per group.

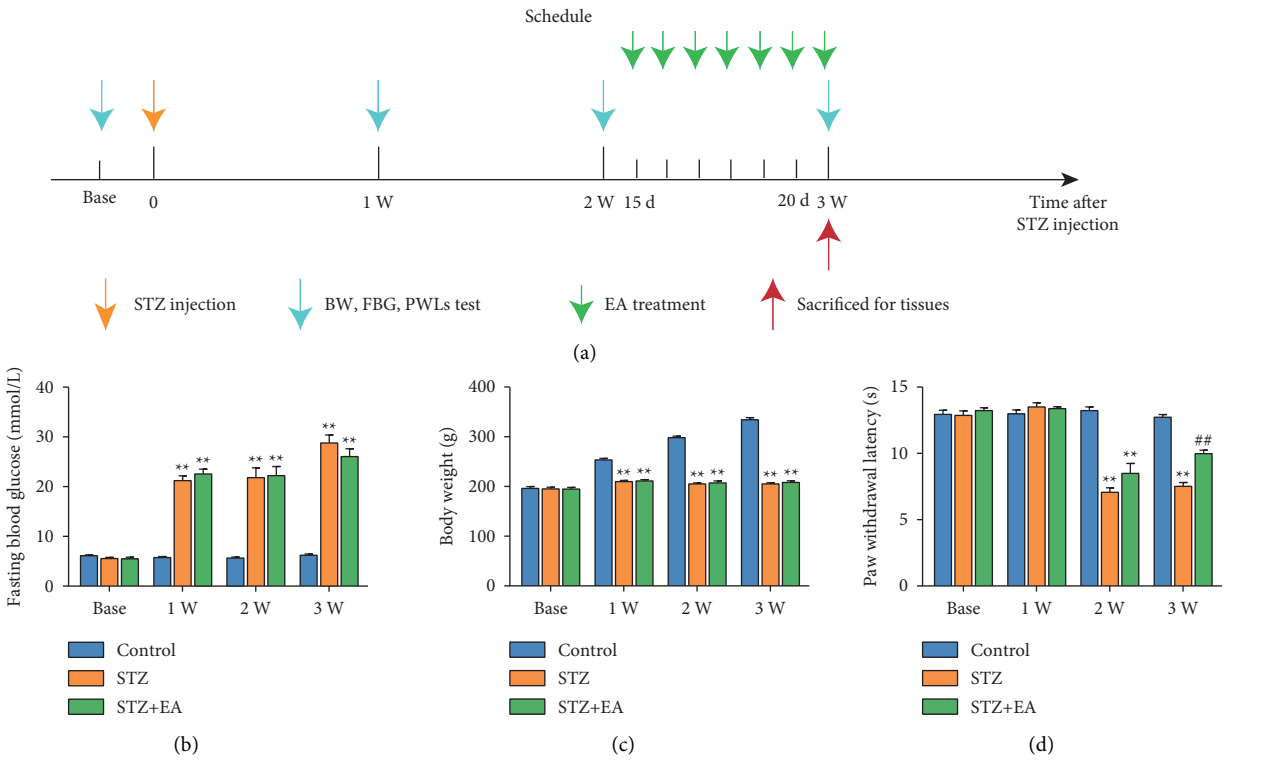

Figure 6: EA attenuated thermal hyperalgesia in a rat model of DNP. (a) Experimental design for establishment of DNP rat model and EA treatment. Time course effect of STZ and EA treatment on FBG (b), BW (c) and PWL (d). Data are presented as mean ± SEM, $n = 10$ per group. $^{**}P < 0.01$ vs. Control group; $^{\#\#}P < 0.01$ vs. STZ group.

to the SCDH [33, 34]. Many changes of protein in DRG and SCDH are involved in neuropathic pain [35–37].

Previous studies showed that PKC is involved in the transmission of neuropathic pain including DNP [14, 38, 39]. PKC is a phospholipid-dependent serine/threonine kinase family. This family comprises 13 isoenzymes that can be activated by extracellular signals [40]. The active state of PKC is p-PKC, which is a phosphorylated state [41, 42] and is implicated in various roles [43]. TRPV1 is a nonselective ligand-gated cationic channel assembled as a

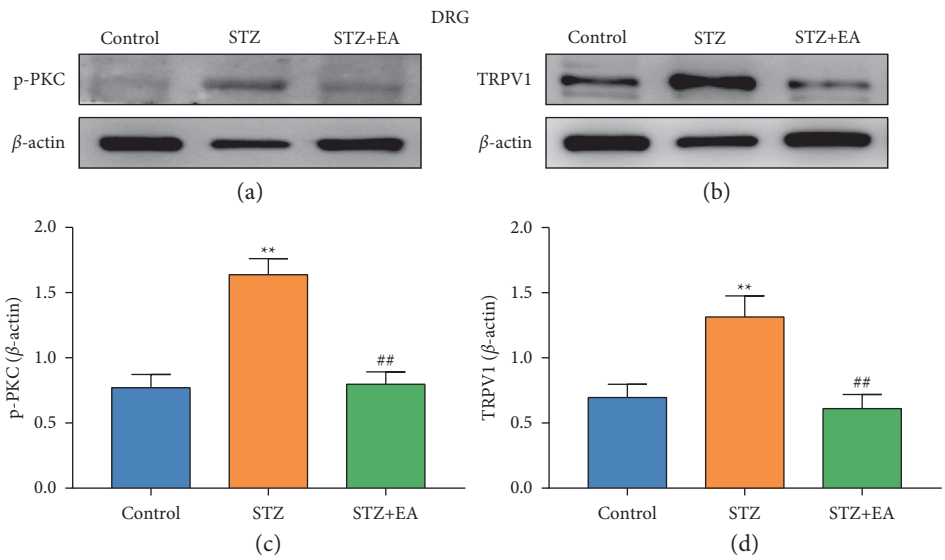

Figure 7: Protein expression of p-PKC and TRPV1 in DRG of DNP rats after EA treatment. (a, b) Representative images of WB result of p-PKC and TRPV1 in DRG from different groups. (c, d) WB showed the decreased p-PKC and TRPV1 expression in DRG in STZ + EA group rats compared to DNP rats. Data are presented as mean ± SEM, $n = 5$ per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. STZ group.

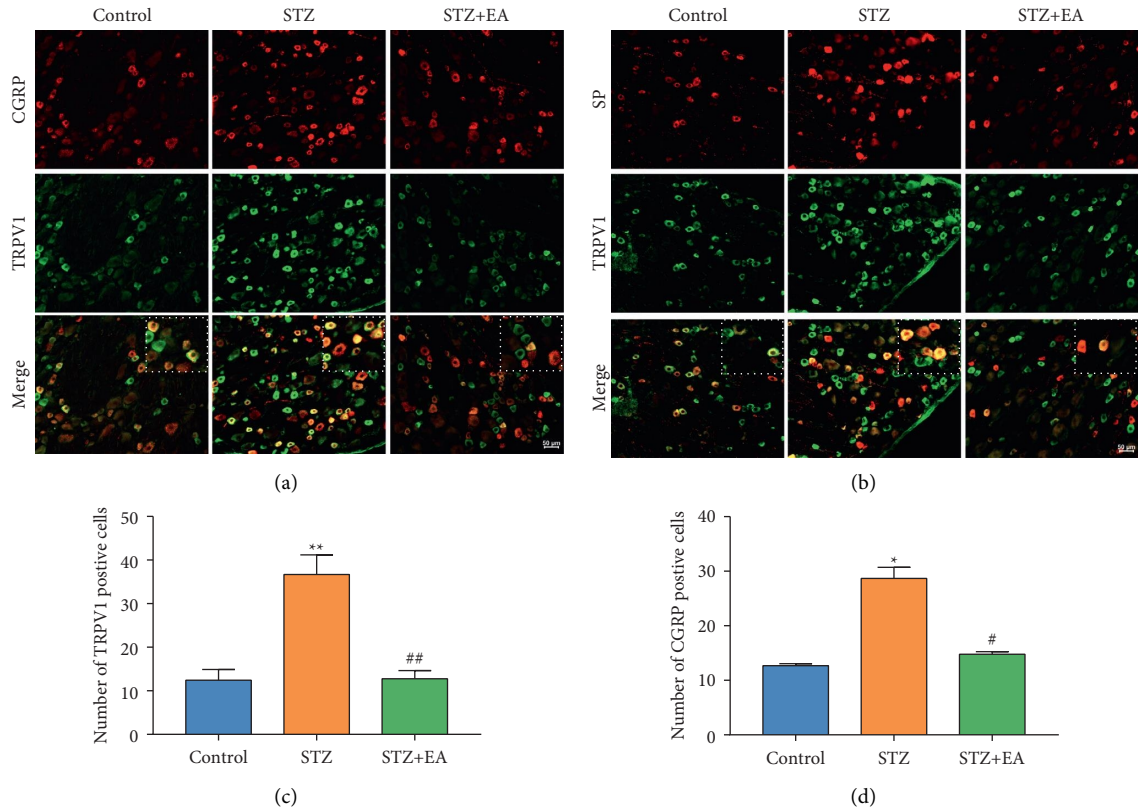

Figure 8: Continued.

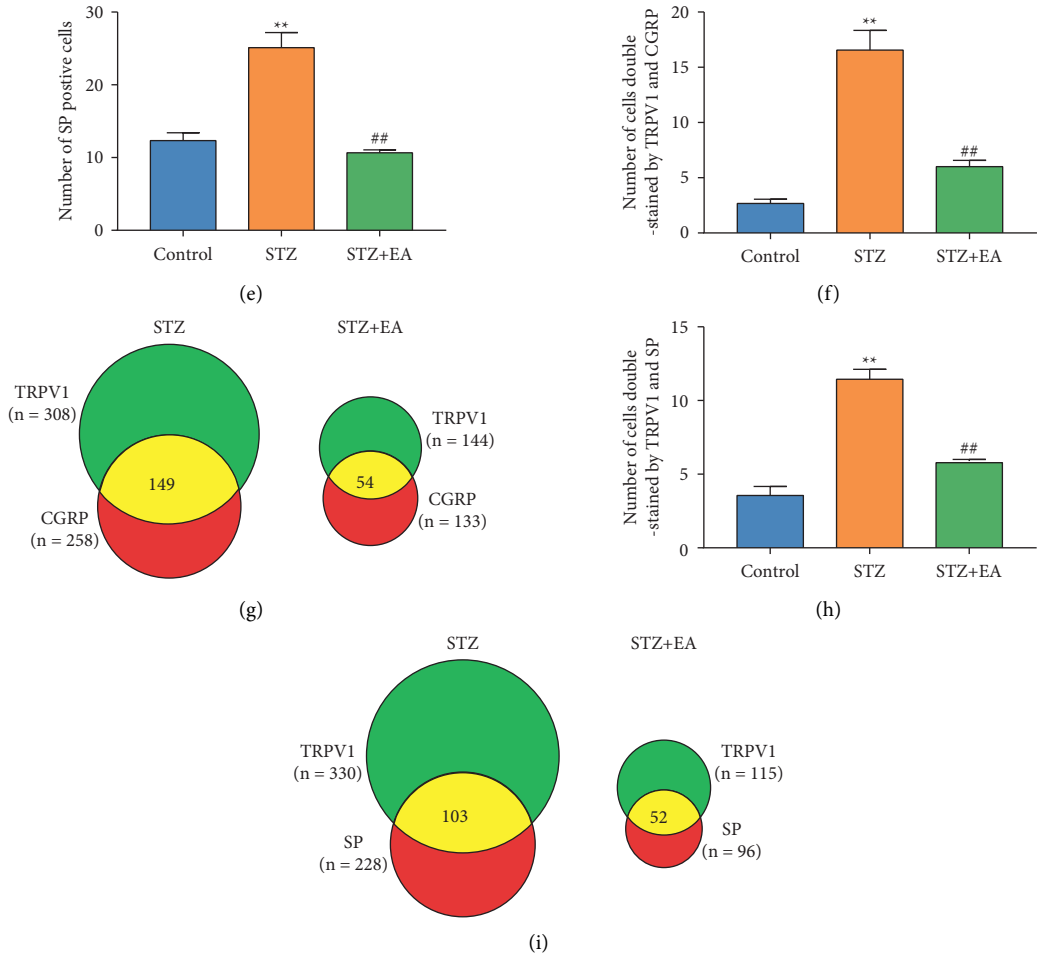

Figure 8: IF results of TRPV1, SP, and CGRP in DRG of DNP rats after EA treatment. (a) Representative images of IF of CGRP (red) and TRPV1 (green) in DRG from different groups. Scale bar: 50 μm. (b) Representative images of IF of SP (red) and TRPV1 (green) in DRG from different groups. Scale bar: 50 μm. (c) Number of TRPV1 positive cells in DRG from different groups. (d) Number of CGRP positive cells in DRG from different groups. (e) Number of SP positive cells in DRG from different groups. (f) Number of cells double stained by TRPV1 and CGRP in DRG from different groups. (g) The Venn diagram shows the number of cells double stained with TRPV1 and CGRP in rat L4-L6 DRGs from various groups. $n = 3$ rats. (h) Number of cells double stained by TRPV1 and SP in DRG from different groups. (i) The Venn diagram shows the number of cells double stained with TRPV1 and SP in rat L4-L6 DRGs from various groups. $n = 3$. Scale bars = 50 μm. Data are presented as mean ± SEM, $n = 3$ per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. STZ group.

homotetramer and widely distributed in SCDH and DRGs [12, 44, 45]. TRPV1 receives various pain-causing stimuli such as noxious heat and diverse chemical irritants or toxins [46–48]. TRPV1 is an effective target for control of neuropathic pain [49]. A previous study reported that the expression of p-PKC and TRPV1 in neurogenic inflammation was significantly upregulated in DRGs [12]. This is consistent with the results of the present study. In the current study, WB analysis showed an increase in p-PKC and TRPV1 expression levels in DRGs and SCDH of DNP rats. SP and CGRP are coexpressed in primary sensory nerves. IF results showed that the number of TRPV1-positive and CGRP-positive in DRG were increased significantly starting 1 week after STZ injection. SP-positive, TRPV1/CGRP-positive, and TRPV1/SP-positive cells in DRG were significantly increased starting 2 weeks after STZ injection. P-PKC, CGRP, and SP in SCDH are significantly elevated starting from the first week, while TRPV1 in SCDH was significantly increased from the 2 weeks. This may be why thermal hyperalgesia developed at 2 weeks rather than 1 week after STZ injection. Sensory nerves endings are released to transmit pain signals when they are activated by stimuli [50]. SP and CGRP are expressed after activation of TRPV1 [51]. In the present study, immunofluorescence double staining was performed to explore colocalization of TRPV1 with SP and CGRP and to verify the upregulation of SP and CGRP expression in DNP. The findings indicated that STZ injection induces expression of p-PKC, TRPV1, SP, and CGRP in DRGs and SCDH upregulated.

Currently, clinical studies have failed to prove the effectiveness of treatment with less adverse effects for patients with neuropathic pain [52]. A previous study reported that berberine blocks PKC channels to inhibit TRPV1 activation, thus improving DNP [14]. EA is a combination of acupuncture and electric current and is an effective approach for relieving neuropathic pain [53]. A previous study reported

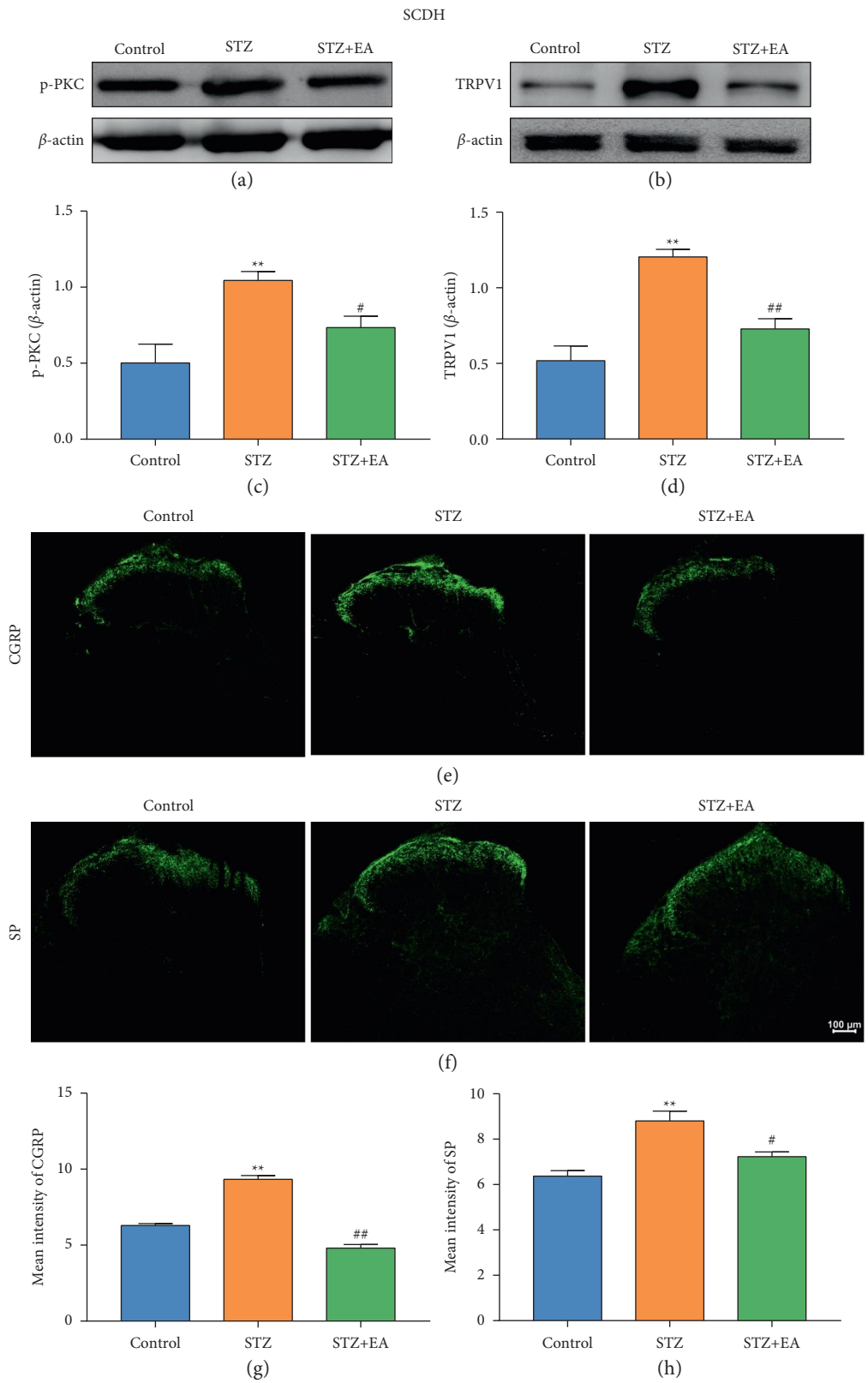

Figure 9: Expression of p-PKC and TRPV1 in SCDH of DNP rats after EA treatment. (a, b) Representative images of WB result of p-PKC and TRPV1 in SCDH from different groups. (c, d) WB showed the decreased p-PKC and TRPV1 expression in SCDH in STZ + EA group rats compared to DNP rats. Data are presented as mean ± SEM, $n = 5$ per group. (e) Representative images of IF of CGRP staining in SCDH from different groups. (f) Representative images of IF of SP staining in SCDH from different groups. (g) Mean intensity analysis of CGRP in SCDH from various groups. (h) Mean intensity analysis of SP in SCDH from different groups. Scale bars = 100 μm. Data are presented as mean ± SEM, $n = 3$ per group. $^{**}P < 0.01$ vs. Control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. STZ group.

that 2 Hz EA has better analgesic effects than 100 Hz EA [20]. The analgesic effect of 2 Hz EA has also been demonstrated in other pain models [54, 55]. Numerous studies have shown that EA intervention on ST36 and BL60 in rats can alleviate different types of neuropathic pain [56–58]. The preliminary study of our research group showed that the intervention of EA of ST36 and BL60 can effectively alleviate diabetic neuropathic pain [59, 60]. Thus, in the present study, the acupoints of ST36 and BL60 were selected to study the analgesic mechanism of EA. EA intervention in rats with neck-incision pain upregulated thermal pain thresholds and downregulated CGRP and SP expression in the dorsal aspect of the cervical spinal cord [61]. In addition, EA ameliorated nociceptive sensitization in rats with chronic pain and reduced TRPV1 expression on DRG [56]. EA treatment improved thermal hyperalgesia. EA treatment significantly reduced the overexpression of p-PKC, TRPV1, SP, and CGRP in SCDH and DRGs of DNP rats. These findings all support that EA may be a promising therapeutic option for DNP. However, further clinical studies are needed to comprehensively evaluate the therapeutic potentials of EA on DNP patients.

5. Conclusion

In conclusion, p-PKC, TRPV1, SP, and CGRP in DRGs and SCDH were significantly elevated after STZ-induced neuropathic pain. EA treatment alleviates STZ-induced DNP, which may be associated with downregulation of p-PKC, TRPV1, SP, and CGRP in DRGs and SCDH. However, the specific mechanism of action of EA was not explored in the current study. Further studies should be conducted to determine the role of p-PKC/TRPV1 in DNP.

Abbreviations

BW: Body weight
CGRP: Calcitonin gene-related peptide
DNP: Diabetic neuropathic pain
DRG: Dorsal root ganglion
EA: Electroacupuncture
FBG: Fasting blood glucose
IF: Immunofluorescence
i.p: Intraperitoneal
PKC: Protein kinase C
p-PKC: Phosphorylated protein kinase C
PWL: Paw withdrawal latency
SCDH: Spinal cord dorsal horn
SEM: Standard error of the mean
SP: Substance P
STZ: Streptozotocin
TRPV1: Transient receptor potential vanilloid-1
WB: Western blot.

Data Availability

Key data are included in the diagrams and the main text. Datasets used and analyzed in this study are available upon request from the corresponding author.

Ethical Approval

All animal experiments and studies were approved by the Animal Care and Welfare Committee of Zhejiang University of Traditional Chinese Medicine, China (approval no. IACUC-20190805-04).

Conflicts of Interest

The authors declare no conflicts of interest for this work.

Authors' Contributions

Yi-qi Ma and Qun-qi Hu contributed equally to this work as co-first authors.

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Review Article

Comparison of Efficacy of Acupuncture-Related Therapy in the Treatment of Postherpetic Neuralgia: A Network Meta-Analysis of Randomized Controlled Trials

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Background. Postherpetic neuralgia (PHN) is the most common sequela of herpes zoster, and the efficacy of the treatment regimens recommended in the guidelines is not entirely reliable. Acupuncture and moxibustion are widely used complementary alternative therapies that have a positive effect on the treatment of PHN. However, there are various forms of acupuncture and moxibustion, and there are differences in efficacy between the different forms. *Methods*. The retrieval work of randomised controlled trials (RCTs) of acupuncture for PHN in English databases (including PubMed, Cochrane Library, Embase, Web of Science) and Chinese databases (including China National Knowledge Infrastructure (CNKI), WeiPu database, WanFang database, and China Biomedical Literature Database) were conducted from the time of database creation to June 2022. Literature screening, data extraction, and evaluation of risk of bias for the included studies were carried out independently by two researchers, and data analysis was performed using Stata 14.2 software. *Results*. A total of 30 RCTs including 2138 patients with PHN were included. In terms of pain improvement, acupoint embedding + Western medicine group, bloodletting-cupping group, and bloodletting-cupping + Western medicine group ranked top. In terms of total efficiency, acupuncture + Western medicine group, bloodletting-cupping + Western medicine group, and acupoint embedding group ranked top. There were no statistically significant differences in the incidence of adverse events between treatment regimens. *Conclusions*. In a comprehensive comparison of the outcome indicators of 14 different treatment regimens, we considered acupoint injection + Western medicine and bloodletting-cupping + Western medicine to be the best combinations for the treatment of PHN. Due to the limitations of the study, the above conclusions still need to be validated in further multi-centre, large-sample prospective randomised controlled clinical trials.

1. Introduction

PHN is a neuropathic pain that persists for 1 month or more after the healing of the herpes zoster (HZ) rash and is the most common complication of herpes zoster [1]. The nature of pain in PHN is varied and can be burning, electric shock, knife-like or hand-needle pain, intermittent or continuous [2]. Approximately 18~41% of patients with HZ experience PHZ, a painful condition that can last for months or even years [3], during which physical, emotional, and social functioning are affected [4]. PHZ also adds to the medical burden at the individual and societal level [1].

Current treatment for PHN includes both pharmacological and interventional treatments, with pharmacological treatment being the most basic and commonly used method [5]. The drugs currently recommended for first-line treatment of PHN are calcium channel modulators (e. g. pregabalin, gabapentin, tricyclic antidepressants (TCAs) and lidocaine patch 5%) [6, 7]. However, these drugs are not suitable for long-term use and their

efficacy is not entirely reliable [8]. Other treatments include opioid analgesics, tramadol, topical capsaicin and botulinum toxin type A, but the long-term efficacy and safety of these drugs is uncertain [1, 9]. Therefore, how to optimise PHN treatment strategies is a matter of concern to clinicians.

Acupuncture-related therapy, based on meridian theory, is a traditional treatment modality of Chinese origin that plays an important role in the field of complementary and alternative therapies. A 2010 survey of global research trends in acupuncture [10] showed that pain management with acupuncture has been the most prevalent area of research and that acupuncture-related therapies have been widely used in the treatment of joint, muscle, and nerve-related pain and are safe and effective [11–14]. A large number of clinical studies on acupuncture-related therapies for the treatment of PHN have been conducted in China and abroad, and there are various forms of acupuncture, including acupuncture, moxibustion, electroacupuncture, fire acupuncture, and blood-letting [8]. Recent systematic evaluations have confirmed that acupuncture-related therapies (including fire acupuncture, acupuncture, electroacupuncture, and moxibustion) are effective for PHN and that they can reduce pain intensity, relieve anxiety, and improve quality of life in patients with PHN [15–17]. As these studies have mainly focused on the comparison of acupuncture therapies with traditional drug therapies, there is a lack of comparison of efficacy between different acupuncture therapies, and therefore, there is still controversy in clinical practice as to which acupuncture therapy is the best choice. Network meta-analysis (NMA) is a further development of traditional pairwise meta-analysis [18]. Based on current clinical research data, the NMA can complete both direct and indirect comparisons between different acupuncture therapies and further synthesise the results of direct and indirect comparisons to produce a ranking of the efficacy of different acupuncture treatments [11]. This study therefore used Network Meta-analysis to compare the efficacy of different acupuncture and moxibustion therapies in the treatment of PHN and to provide evidence for choosing the optimal combination for the clinical treatment of PHN.

2. Methods

2.1. Study Registration. This network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for NMA guidelines [19]. This research programme has been registered on PROSPERO at https://www.crd.York.ac.uk/prospero/#recordDetails; registration number: CRD42022324870.

2.2. Inclusion and Exclusion Criteria

2.2.1. Type of Study. This study included parallel randomised controlled trials (RCTs) published in Chinese or English, which were subject to the limitations of the intervention. There was no requirement for the study to be blinded.

2.2.2. Study Population. Patients included in the study met the American Academy of Family Physicians' diagnostic criteria for PHN [2], or other accepted diagnostic guidelines for pain lasting 30 days to more than 6 months after healing of the HZ lesions. There were no restrictions on the gender or age of the patients.

2.2.3. Interventions. The treatment group was treated with different acupuncture therapies alone or in combination with Western medicine, which were defined as acupoint stimulation techniques guided by the meridian theory of Chinese medicine, including any of the following therapies: conventional acupuncture, warm acupuncture, electroacupuncture, fire acupuncture, bloodletting-cupping, moxibustion, acupoint burial, acupoint injection; the control group was Western medicine, which had to be first-line drugs recommended by guidelines for the treatment of PHN [6], including calcium ion channel modulators (e. g. pregabalin, gabapentin, tricyclic antidepressants (TCAs) and lidocaine patch 5%).

2.2.4. Outcome Indicators. Primary outcome indicators: the primary objective of this study was to assess pain control, and pain measures included the Visual Analogue Scale (VAS) and Numerical Rating Scale.

Secondary outcome indicators. ① The efficiency rate, which was based on the evaluation of the overall efficacy and the evaluation criteria based on the Criteria of Diagnosis and Therapeutic Effects of Diseases and Syndromes in Traditional Chinese Medicine [20] and the Guiding Principles for Clinical Research of New Chinese Medicines [21]; ② the occurrence of adverse effects.

Exclusion criteria. ① The presence of other painful conditions in the study population; ② lack of primary outcome indicators; ③ treatment protocols that included a combination of two or more acupuncture therapies, such as acupuncture combined with moxibustion, electroacupuncture combined with moxibustion, etc.; ④ duplicate published studies; and ⑤ studies for which complete data were not available in the article and relevant data were still not available after contacting the authors.

2.3. Literature Search Strategy. We searched Chinese databases (China National Knowledge Infrastructure (CNKI), WanFang Data, VIP, and CBM) and English databases (PubMed, Embase, Web of Science, and the Cochrane Library) for RCTs of acupuncture-related therapies for PNH. We used the method of subject terms combined with free words, and the Chinese search terms included "Shou Zhen" (acupuncture), "Dian Zhen" (electroacupuncture), "Wen Zhen Jiu" (warm acupuncture), "Huo Zhen" (fire acupuncture), "Ci Luo Ba Guan" (bloodletting-cupping), "Ai Jiu" (moxibustion), "Xue Wei Mai Xian" (acupoint embedding), "Xue Wei Zhu She" (acupoint injection), and "Dai Zhuang Pao Zhen Hou Yi Shen Jing Tong" (post-herpetic

neuralgia). English search terms include "acupuncture," "electroacupuncture," "warm needle," "fire needle," "bloodletting," "moxibustion," "acupoint embedding," "acupoint injection," "Postherpetic neuralgia," "PHN." The PubMed database search strategy is shown in Table 1.

2.4. Literature Selection. The retrieved literature was imported into EndNote X9 software and checked for duplicates. After excluding duplicates, an initial screening was carried out by reading the abstracts to exclude irrelevant studies, and the remaining studies were further assessed by reading the full text, and finally data extraction was completed for those studies that met the inclusion criteria. All of the work above was done by two independent researchers, and where there was disagreement between the two researchers, a third researcher assisted in the judgement. Data extraction included title, author, date of publication, sample size, details of the intervention, details of the control measure, duration of treatment, and outcome indicators. For multiarm studies reporting different types of acupuncture interventions, data were extracted from all relevant arms. For pain scores, the mean and standard deviation of baseline and posttreatment change scores (defined as the baseline score minus the posttreatment score) were taken.

2.5. Risk of Bias Evaluation of Included Studies. Two independent researchers evaluated the included studies back-to-back by means of the Cochrane Systematic Evaluation Manual version 5.1.0 RCT Risk of Bias Assessment Tool [22]. The elements of the evaluation included random sequence generation, outcome allocation concealment, blinding of participants and personnel, blinding of assessment, incomplete outcome data, selective reporting bias and other bias. The final decision was "high risk," "low risk," or "unclear".

2.6. Statistical Analysis

2.6.1. Direct Comparison. Direct comparative meta-analysis was performed using Stata 14.2 software. For continuous variables, analysis was carried out using the standard mean difference (SMD), and for dichotomous variables, relative risk (RR) was used. Heterogeneity between the results of the included studies was analysed using the χ^2 test, while the magnitude of heterogeneity was determined quantitatively in conjunction with I^2. If $P \geq 0.10$, $I^2 < 50\%$, there was no significant heterogeneity between studies and a fixed-effects model was used for meta-analysis; if $P < 0.10$, $I^2 \geq 50\%$, heterogeneity between studies was considered significant and a random-effects model was used for meta-analysis.

2.6.2. Reticulated Meta-Analysis. The Stata 14.2 software was used to plot the net relationship between direct and indirect comparisons between the outcomes of the different treatment measures. For studies with three or more arms, they were first divided into pairwise contrast combinations. The included studies were also tested for consistency and non-consistency, and local inconsistency was tested using the nodal split method; $P > 0.05$ was considered good for consistency. For each outcome indicator, the efficacy of the interventions was ranked using the surface under the cumulative ranking (SUCRA) values. The publication bias of included studies was tested by comparison-corrected funnel plots.

3. Results

3.1. Literature Search Results. A total of 5090 relevant literature was retrieved, and after initial screening and re-screening, 30 RCTs were finally included, comprising a total of 2138 patients. The literature screening process is shown in Figure 1.

3.2. Basic Characteristics of the Included Studies. Of the 30 studies included, three involved electroacupuncture; one involved electroacupuncture combined with Western medicine; two involved warm acupuncture, six involved bloodletting-cupping; four involved bloodletting-cupping combined with Western medicine; four involved acupuncture; four involved acupuncture combined with Western medicine; three involved fire acupuncture; one involved acupoint injection, two involved acupoint injections combined with Western medicine; two involved acupuncture burials; one involved acupuncture burial combined with Western medicine; one involved blood prick; and 30 involved Western medicine. There were two three-armed studies [23, 24], one four-armed study [25], and 27 two-armed studies [26–52]. All studies reported pain scores [23–52], 23 studies reported overall effectiveness [23, 25, 26, 28–38, 40, 42–44, 46, 47, 49, 50, 52] and 14 studies [25, 26, 31, 33, 36, 39, 43–45, 47–49, 51, 52] reported adverse effects. The basic characteristics of the included studies are shown in Table 2 and the characteristics of the interventions are shown in Table 3.

3.3. Results of the Risk of Bias Evaluation of the Included Studies. ① Random sequence generation: 17 studies [23, 25, 28, 29, 31, 32, 35, 36, 39–41, 44, 45, 48, 49, 51, 52] used random number tables, three studies [30, 34, 46] used computer-generated random numbers, two studies [37, 42] used consultation sequences and the remaining eight studies [24, 26, 27, 33, 38, 43, 47, 50] referred to "random" only. ② Allocation concealment: 4 studies [23, 30, 48, 52] used sealed opaque envelopes; 2 studies [37, 42] used order of attendance and the remaining 24 studies did not mention allocation concealment. ③ Blinding of patients, trialists: none of the studies were double-blinded due to the limitations of the intervention modality. ④Blinding of outcome assessors: none of the studies mentioned blinding of outcome assessors; ⑤Incomplete outcome data, selective reporting, other bias: all studies had complete outcome data, with no selective reporting or other bias. The results of the risk of bias evaluation are shown in Figure 2.

Table 1: PubMed database search strategy.

Number	Search terms
#1	Acupuncture [MeSH]
#2	Acupuncture [title/abstract]
#3	Cupping [title/abstract]
#4	Electroacupuncture [title/abstract]
#5	Warm needle [title/abstract]
#6	Fire needle [title/abstract]
#7	Blood-letting [title/abstract]
#8	Moxibustion [MeSH]
#9	Moxibustion [title/abstract]
#10	Auricular application pressure [title/abstract]
#11	Auricular needle [title/abstract]
#12	Acupoint embedding [title/abstract]
#13	Acupoint injection [title/abstract]
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	Neuralgia, postherpetic [MeSH]
#16	Postherpetic neuralgia [title/abstract]
#17	#15 OR #16
#18	#14 AND #18

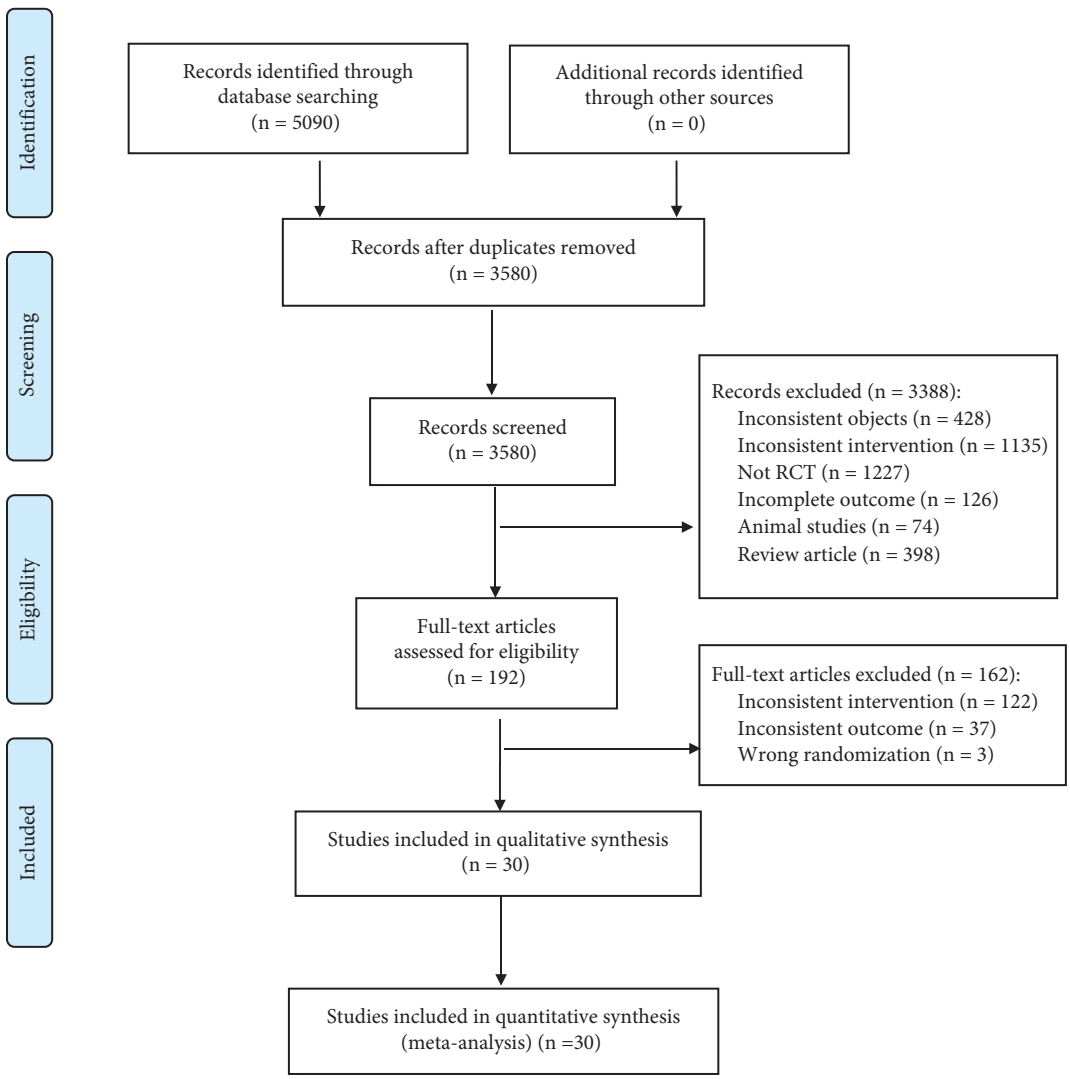

Figure 1: Literature screening process.

Table 2: Basic characteristics of included studies.

Included studies	Random method	Sample (T/C)	Gender (M/F)	Age (years)	Course (months)
Huang [31]	Random number table	30/30	T: 14/16 C: 13/17	T: 65.20 ± 9.93 C:66.07 ± 9.68	T: 4.03 ± 6.34 C: 3.90 ± 4.80
Liu [26]	Unclear	38/34	T: 18/20 C: 13/21	T: 68.32 ± 9.74 C: 69.21 ± 9.21	T: 1.58 ± 1.18 C: 1.53 ± 1.02
Zhang [50]	Unclear	63/63	T: 35/28 C: 34/29	T: 62.70 ± 6.83 C: 62.54 ± 6.78	T: 5.13 ± 0.81 C: 5.10 ± 0.79
Deng [29]	Random number table	43/43	T: 31/12 C: 28/15	T: 55.40 ± 7.93 C: 21.58 ± 4.13	T: 22.17 ± 4.44 C: 21.58 ± 4.13
Zhai [30]	Computer generated random numbers	40/40	T: 17/23 C: 19/21	T: 63.7 ± 6.8 C: 62.4 ± 7.6	T: 8.50 ± 3.46 C: 8.43 ± 4.36
Ding [51]	Random number table	57/58	T: 25/32 C: 27/31	T: 59.33 ± 6.25 C: 62.45 ± 9.23	T: 3.71 ± 0.49 C: 3.49 ± 0.63
Wang H 2014	Unclear	21/21/21	Unclear	Unclear	Unclear
Chen [27]	Unclear	27/27	T: 16/11 C: 14/13	T: 62.18 ± 7.98 C: 63.25 ± 7.49	Unclear
Zhou YN 2018	Random number table	30/30	T: 14/16 C: 12/18	T: 52.78 ± 8.12 C: 53.34 ± 7.60	T: 6.85 ± 4.48 C: 6.62 ± 4.13
Zhang [25]	Random number table	20/20/20/20	T1: 8/12 T2: 13/7 T3: 12/8 C: 9/11	T1: 60 ± 7 T2: 60 ± 7 T3: 61 ± 7 C: 60 ± 8	T1: 1.62 ± 0.54 T2: 1.76 ± 0.43 T3: 1.59 ± 0.68 C: 1.65 ± 0.51
Li [33]	Unclear	30/31	T: 13/17 C: 14/17	T: 53 ± 12 C: 56 ± 10	T: 1.5 ± 1.1 C: 1.7 ± 0.9
Liu [38]	Unclear	31/31	T: 14/17 C: 15/16	T: 59.90 ± 9.07 C: 60.25 ± 8.79	T: 55.22 ± 15.01 (days) C: 57.58 ± 15.09 (days)
Liu B 2020	Computer generated random numbers	38/27	T: 21/17 C: 16/11	T: 64.5 ± 3.5 C: 67.5 ± 3.8	T: 4.1 ± 1.2 C: 3.3 ± 0.6
Wang [35]	Random number table	35/35	T: 16/19 C: 17/18	T: 57.8 C: 58.6	T: 62.73 ± 10.15 (days) C: 61.82 ± 9.48 (days)
Liu [37]	Order of consultation	40/40	T: 22/18 C: 15/15	T: 50.25 ± 10.17 C: 50.18 ± 10.38	Unclear
Liu [39]	Random number table	62/58	T: 37/25 C: 35/23	T: 26.30 ± 7.66 C: 26.66 ± 7.28	Unclear
Qing L 2019	Random number table	25/25	Unclear	Unclear	Unclear
Tian [41]	Random number table	34/34	T: 14/18 C: 16/16	T: 61 C:61	T: 4 C: 4
Liu [42]	Order of consultation	35/33	T: 18/17 C: 19/14	T: 49 C: 52	Unclear
Wang [43]	Unclear	41/36	Unclear	Unclear	Unclear
Xie YJ 2013	Random number table	40/40	T: 21/19 C: 18/22	T: 65.3 ± 10.4 C: 65.8 ± 10.8	Unclear
Li LP 2019	Random number table	30/29	T: 16/14 C: 14/15	T: 59 ± 11 C: 57 ± 13	T: 1.1 ± 0.15 (years) C: 1.2 ± 0.13 (years)
Yang [46]	Computer generated random numbers	34/34	T: 22/12 C: 23/11	T: 56.8 ± 14.9 C: 54.3 ± 12.4	T: 4.9 ± 3.8 C: 5.6 ± 3.4
Chen [28]	Random number table	30/28	T: 15/15 C: 13/15	T: 55.17 ± 10.88 C: 52.93 ± 10.4	T: 6.23 ± 1.61 C: 6.41 ± 1.92
Wang [47]	Unclear	40/40	T: 21/19 C: 20/20	T: 59.43 ± 5.27 C: 60.13 ± 4.29	T: 5.73 ± 1.16 C: 5.98 ± 1.03
Zhang [48]	Random number table	45/45	T: 12/33 C: 11/34	T: 48.49 ± 4.29 C: 46.39 ± 6.38	Unclear
Zhang [23]	Random number table	20/20/19	T1: 5/15 T2: 9/11 C: 11/8	T1: 62.55 ± 7.48 T2: 64.2 ± 10.81 C: 66.79 ± 11.25	Unclear
Zhang [49]	Random number table	31/30	T: 16/15 C: 17/13	T: 61.69 ± 8.43 C: 61.42 ± 7.96	T: 7.43 ± 1.49 C: 7.68 ± 1.52
Lin [36]	Random number table	32/31	T: 12/18 C: 13/17	T: 54.63 ± 4.57 C: 54.03 ± 5.5	T: 7.33 ± 6.24 C: 7.57 ± 5.89

Table 2: Continued.

Included studies	Random method	Sample (T/C)	Gender (M/F)	Age (years)	Course (months)
Zhong [52]	Random number table	33/33	T: 16/17 C: 15/18	T: 60.03 ± 3.9 C: 59.55 ± 5.36	T: 3.61 ± 1 C: 3.58 ± 1

Notes. T, Treatment group; C, Control group; M, Male; F, Female.

3.4. Directly Compared meta-Analysis Results

3.4.1. Pain Scores. In a direct comparison regarding pain scores, meta-analysis showed that the pain score of warm acupuncture, electroacupuncture, electroacupuncture + Western medicine, acupuncture + Western medicine, bloodletting-cupping, bloodletting-cupping + Western medi cine, fire acupuncture, and acupoint embedding groups were superior to that of the Western medicine group ($P < 0.05$), while the scores in acupuncture and acupuncture point injection + Western medicine groups did not differ from the Western medicine group ($P > 0.05$). Descriptive analysis showed that both the acupoint injection and acupoint embedding groups were superior to the Western medicine group ($P < 0.05$). The acupuncture group was superior to the electroacupuncture group, the acupuncture + Western medicine group was superior to the acupuncture group ($P < 0.05$), and there was no difference between the fire acupuncture + Western medicine group and the Western medicine group, the fire acupuncture group and the bloodletting-cupping group compared to the acupuncture group ($P > 0.05$), see Table S2 in the supplementary material.

3.4.2. Total Efficiency. In a direct comparison regarding pain scores, meta-analysis showed that the acupuncture, acupuncture + Western medicine, fire acupuncture, bloodletting-cupping, acupoint embedding groups were all superior to the Western medicine group ($P < 0.05$), with no difference in the electroacupuncture group compared to the Western medicine group. Descriptive analyses of acupoint embedding + Western medicine compared with Western medicine, fire acupuncture, bloodletting-cupping, and electroacupuncture compared with acupuncture showed no difference ($P > 0.05$), see Table S2 in the supplementary material.

3.4.3. Adverse Reactions. In a direct comparison regarding adverse reaction rates involving 10 interventions (warm acupuncture, acupuncture, acupuncture + Western medicine, bloodletting-cupping, bloodletting-cupping + Western medicine, electroacupuncture, electroacupuncture + Western medicine, acupoint injection, acupoint injection + Western medicine, and acupoint embedding) versus Western medicine, none of their adverse reaction rates differed from those of Western medicine ($P > 0.05$), see Table S2 in the supplementary material.

3.4.4. Heterogeneity Analysis. In the meta-analysis of direct comparisons, there was heterogeneity in some of the results. Analysis of the raw data revealed possible methodological heterogeneity due to the inclusion of studies with less description of blinding and allocation concealment, as well as possible clinical heterogeneity due to factors such as inclusion of populations, acupuncture points, and manipulation methods, but as the original studies did not specify these details and the small number of studies for some of the outcomes, further subgroup analysis could not be performed to explore sources of heterogeneity. However, we found by sensitivity analysis that the results were stable after excluding either study; see sensitivity analysis figures in the supplementary material (Figure S1~S19). We could therefore ignore this heterogeneity and used a random-effects model for Meta-analysis.

3.5. Comparative Results of Reticulated Meta-Analysis

3.5.1. Evidence Network Map. Thirty included studies reported pain scores [23–52] involving 14 treatment regimens, forming a total of 6 closed loops; 12 studies reported overall effectiveness [23, 25, 28–30, 35, 37, 38, 42, 47, 49, 52] involving 9 treatment regimens, forming a total of 5 closed loops; and 14 studies [25, 26, 31, 33, 36, 39, 43–45, 47–49, 51, 52] reported adverse effects involving 11 treatment regimens, with no closed loops formed. The thicker the line between the two, the greater the number of studies between the two measures, the larger the node and the larger the sample size of studies involving this intervention, as shown in Figures 3–5.

3.5.2. Results of Reticulated Meta-Analysis of Pain Scores. Thirty studies reported pain scores [23–52], with inconsistency tests $P = 0.992 > 0.05$, and local inconsistency tests using the nodal split method with $P > 0.05$, showing good agreement between studies and reticulated meta-analysis under the consistency model. The results showed that acupoint injection + Western medicine was superior to acupuncture, acupuncture + Western medicine, electroacupuncture, bloodletting-cupping and Western medicine, and bloodletting-cupping + Western medicine was superior to Western medicine. The rest of the comparisons between the different treatments were not statistically different, see Table 4. The results of the ranking of pain scores were: acupoint injection + Western medicine (97%) > bloodletting-cupping (70.7%) > bloodletting-cupping + Western medicine (59%) > warm acupuncture (55.7) > acupuncture + Western medicine (55.6%) > fire acupuncture (49.8%) > electroacupuncture + Western medicine (46.6%) > acupuncture (46%) > electroacupuncture (43.4%) > acupoint embedding + Western medicine (42.5%) + (40.8%) > acupuncture (35.8%) > Western medicine (20.9%), as shown in Figure 6 for the SUCRA ranking chart.

Table 3: Characteristics of the included study interventions.

Inclusion of literature	Type of research	Interventions		Treatment course (days)	Outcome indicators
		Treatment group	Control group		
Huang [31]	Two-armed	Electroacupuncture: EX-B2, LR1, LR2, ST44, ashi point, six times a week.	Pregabalin capsules: 2 times/day, 75 mg/dose.	14	①②
Liu [26]	Two-armed	Warm acupuncture: Ashi point, once every two days.	Gabapentin capsules: Day 1, 100 mg/dose, 3 times/day; day 2, 200 mg/dose, 3 times/day; day 3, 300 mg/dose, 3 times/day.	10	①②
Zhang [50]	Two-armed	Bloodletting-cupping: Ashi point, once every two days. Pregabalin capsules: 2 times/day, 75 mg/dose.	Pregabalin capsules: 2 times/day, 75 mg/dose.	14	①
Deng [29]	Two-armed	Acupuncture: Ashi point, once a day. Gabapentin capsules: 300 mg/dose, 3 times/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	Gabapentin capsules: 300 mg/dose, 3 times/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	14	①③
Zhai [30]	Two-armed	Acupuncture: GB36, GB35, LI7, ST34, SI6, BL63, BL59, TE 7	Pregabalin capsules: 2 times/day, 75 mg/dose.	35	①③
Ding [51]	Two-armed	Bloodletting-cupping: Ashi point, 3 times a week. Gabapentin capsules: 300 mg/dose, 1 time/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	Gabapentin capsules: 300 mg/dose, 1 time/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	28	①②
Wang H 2014	Three-armed	①Acupuncture: EX-B2, once a day 1, 1 ②Acupuncture: EX-B2, once a day. Gabapentin capsules: 150 mg/dose on day 1, 1 time/day, 150 mg/dose on day 2, 2 times/day, 150 mg/dose on day 3, 3 times/day, with subsequent increases of 150 mg/day every 1 to 2 days (maximum dose 2,400 mg/day)	Gabapentin capsules: 150 mg/dose on day 1, 1 time/day, 150 mg/dose on day 2, 2 times/day, 150 mg/dose on day 3, 3 times/day, with subsequent increases of 150 mg/day every 1 to 2 days (maximum dose 2,400 mg/day)	14	①
Chen [27]	Two-armed	Warm acupuncture: EX-B2, LR3, GB41, ashi point, once every two days.	Carbamazepine: 100 mg/dose, 2 times/day.	28	①
Zhou YN 2018	Two-armed	Fire acupuncture: Heart and diaphragm, 3 times a week	Pregabalin capsules: 3 times/day, 50 mg/dose.	10	①
Zhang [25]	Four-armed	①Fire acupuncture: Ashi point, once every two days. ②Acupuncture: Ashi point, once a day. ③Bloodletting-cupping: Ashi point, 1 time every other day.	Pregabalin capsules: 2 times/day, 150 mg/dose.	30	①②③
Li [33]	Two-armed	Acupoint injection: EX-B2, once a week. Gabapentin capsules: 200–900 mg/day.	Gabapentin capsules: 200–900 mg/day.	28	①②
Liu [38]	Two-armed	Acupuncture point embedding: DU10, once every two days.	Carbamazepine: 100 mg/dose, 3 times/day.	28	①③
Liu B 2020	Two-armed	Acupuncture: EX-B2, BL17, BL18, ST36, LR3, GB34, KI3. Pregabalin capsules: 2 times/day, 150 mg/dose.	Pregabalin capsules: 2 times/day, 150 mg/dose.	14	①
Wang [35]	Two-armed	Stabbing cupping: Ashi point, once every two days.	Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	16	①③
Liu [37]	Two-armed	Bloodletting-cupping: Ashi point, once time every 5 days.	Pregabalin capsules: 2 times/day, 75 mg/dose.	30	①③
Liu [39]	Two-armed	Acupoint injection: EX-B2, once every two days.	Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	28	①②

Table 3: Continued.

Inclusion of literature	Type of research	Interventions		Treatment course (days)	Outcome indicators
		Treatment group	Control group		
Qing L 2019	Two-armed	Bloodletting-cupping: Ashi point, 1 time daily for the first 3 days, 1 time every other day from the 4th day onwards.	Gabapentin capsules: 300 mg/dose, 3 times/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	30	①
Tian [41]	Two-armed	Bloodletting-cupping: Ashi point, once every two days.	Pregabalin capsules: 2 times/day, 150 mg/dose.	16	①
Liu [42]	Two-armed	Bloodletting-cupping: Ashi point, once every two days.	Flupirtine melitrexin: 10.5 mg/dose, 2 times/day; mecobalamin tablets: 0.5 mg/dose, 3 times/day.	28	①③
Wang [43]	Two-armed	Electroacupuncture: EX-B2, once a day. Pregabalin capsules: 150–600 mg/day in 2 or 3 oral doses.	Pregabalin capsules: 150–600 mg/day in 2 or 3 oral doses.	14	①②
Xie YJ 2013	Two-armed	Acupuncture: Ashi point, once every two days; gabapentin capsules: 300 mg orally on day 1, increasing to 600, 900 mg on days 2–3, 1200 mg/day on days 4–6, 1500 mg on day 7 and 1800 mg/day on days 8–42.	Gabapentin capsules: 300 mg orally on day 1, increasing to 600, 900 mg on days 2–3, 1200 mg/day on days 4–6, 1500 mg on day 7 and 1800 mg/day on days 8–42.	42	①②
Li LP 2019	Two-armed	Acupoint injection: Ashi point, once a week; gabapentin capsules: 300 mg orally on day 1, increasing to 900 mg on day 3, gradually increasing to 1800 mg/day.	Gabapentin capsules: 300 mg orally on day 1, increasing to 900 mg on day 3, gradually increasing to 1800 mg/day.	21	①②
Yang [46]	Two-armed	Electroacupuncture: Jiaji and ashi points, once a day.	Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	28	①
Chen [28]	Two-armed	Acupuncture point embedding: EX-B2, once every fortnight. Pregabalin capsules: 2 times/day, 75 mg/dose.	Pregabalin capsules: 2 times/day, 75 mg/dose.	28	①③
Wang [47]	Two-armed	Acupuncture: EX-B2, ashi, ST36. Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	42	①②③
Zhang [48]	Two-armed	Bloodletting-cupping: Ashi point, once every two days. Pregabalin capsules: 2 times/day, 75 mg/dose.	Pregabalin capsules: 2 times/day, 75 mg/dose.	14	①②
Zhang [23]	Three-armed	①Acupuncture: TE6, GB34, ST36, ashi points, once a day. ②Electroacupuncture: TE6, GB34, ST36, ashi points, once a day.	Gabapentin capsules: 300 mg once daily on day 1, 300 mg twice daily on day 2 and 300 mg three times daily after day 3.	20	①③
Zhang [49]	Two-armed	Bloodletting-cupping: Ashi point, once every two days. Pregabalin capsules: 2 times/day, 150 mg/dose.	Pregabalin capsules: 2 times/day, 150 mg/dose.	30	①②③
Lin [36]	Two-armed	Acupoint embedding: EX-B2, ashi points, once every 2 weeks.	Carbamazepine: 100 mg/dose, 2 times/day.	56	①②
Zhong [52]	Two-armed	Fire acupuncture: EX-B2, ashi points, once every two days.	Pregabalin capsules: 2 times/day, 75 mg/dose.	28	①②③

Notes. ① Pain scores; ② Adverse reactions; ③ Total efficiency.

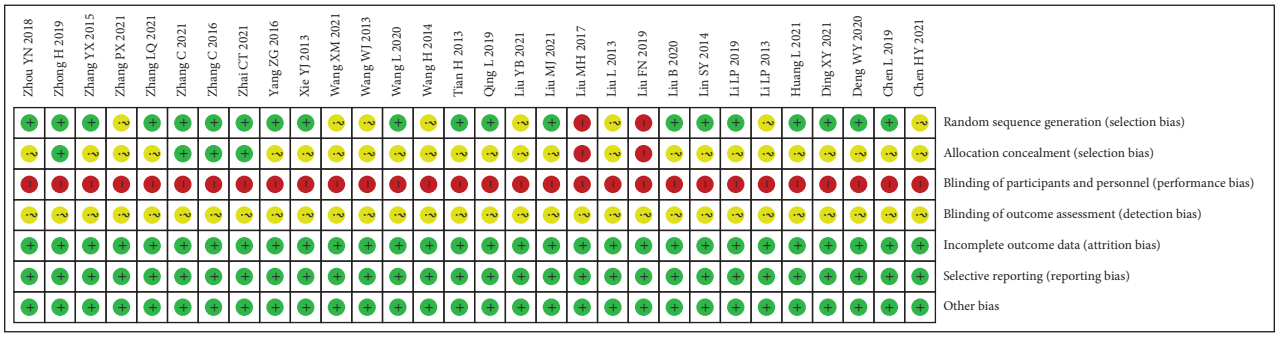

Figure 2: Results of the risk of bias evaluation.

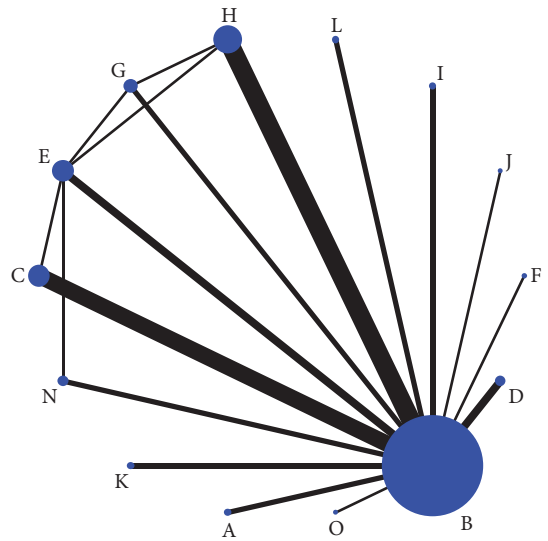

Figure 3: Evidence network graph for pain scores in a reticulated meta-analysis of different acupuncture therapies for PHN. *Notes*. (a) Warm acupuncture; (b) western medicine; (c) acupuncture + western medicine; (d) bloodletting-cupping + western medicine; (e) acupuncture; (f) fire acupuncture + western medicine; (g) fire acupuncture; (h) bloodletting-cupping; (i) acupoint injection + western medicine; (j) acupoint injection; (k) electroacupuncture + western medicine; (l) acupoint embedding; (n) electroacupuncture; and (o) acupoint embedding + western medicine.

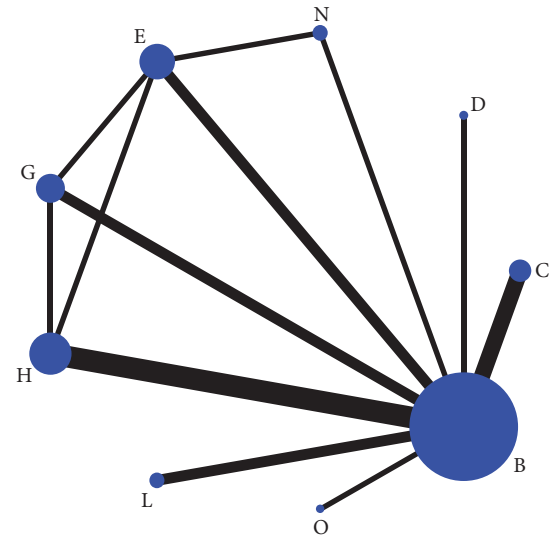

Figure 4: Evidence network diagram of the total efficiency of different acupuncture therapies for PHN in reticulated meta-analysis. *Notes*. (b) western medicine; (c) acupuncture + western medicine; (d) bloodletting-cupping + western medicine; (e) acupuncture; (g) fire acupuncture; (h) bloodletting-cupping; (l) acupoint embedding; (n) electroacupuncture; and (o) acupoint embedding + western medicine.

3.5.3. Results of the Net Meta-Analysis of Total Efficiency. Twelve studies reported overall effective rates [23, 25, 28–30, 35, 37, 38, 42, 47, 49, 52] with inconsistency tests $P = 0.862 > 0.05$ and local inconsistency tests using the nodal split method with $P > 0.05$, showing good agreement between studies and reticulated meta-analysis under the consistency model. The results showed that acupuncture + Western medicine was superior to bloodletting-cupping, bloodletting-cupping + Western medicine and Western medicine, acupuncture was superior to Western medicine, fire acupuncture was superior to Western medicine. The rest of the comparisons between different treatments were not statistically different, see Table 5. The results of the ranking of the total efficiency were: acupuncture + Western medicine (88.3%) > bloodletting-cupping + Western medicine (71.5%) > acupoint embedding (61.9%) > fire acupuncture (60.2%) > acupuncture (60.1%) > bloodletting-cupping (39%) > electroacupuncture (33.5%) > acupoint embedding + Western medicine (25.6%) > Western medicine (10%), see Figure 7 for the SUCRA ranking chart.

3.5.4. Results of the Reticulated Meta-Analysis of Adverse Reactions. Adverse effects were reported in 14 studies [25, 26, 31, 33, 36, 39, 43–45, 47–49, 51, 52]. As they are all indirect comparisons and do not form a closed loop, no consistency test was required. A mesh meta-analysis was performed under the consistency model. The results showed that acupoint injection + Western medicine was superior to acupuncture, acupuncture + Western medicine, bloodletting -cupping, and Western medicine, and acupoint embedding was superior to Western medicine and bloodletting-cupping. The rest of the comparisons between the different treatments were not statistically different, see Table 6. The results of the ranking of the incidence of adverse

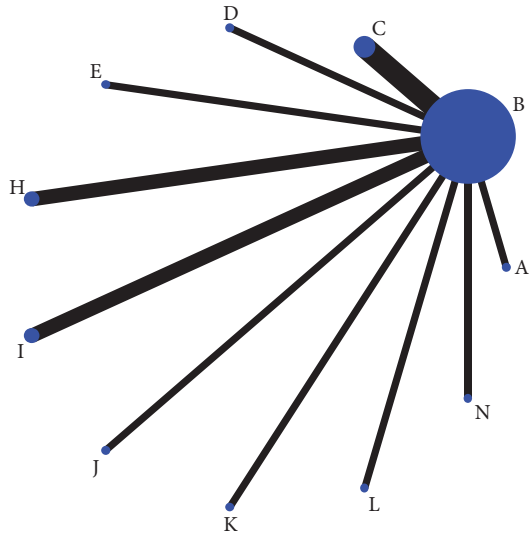

Figure 5: Evidence network diagram for adverse effects of reticulated meta-analysis of different acupuncture treatments for PHN. *Notes*. (a) warm acupuncture; (b) western medicine; (c) acupuncture + western medicine; (d) bloodletting-cupping + western medicine; (e) acupuncture; (f) fire acupuncture + western medicine; (g) fire acupuncture; (h) bloodletting-cupping; (i) acupoint injection + Western medicine; (j) acupoint injection; (k) electroacupuncture + western medicine; (l) acupoint embedding; (n) electroacupuncture; and (o) acupoint embedding + western medicine.

reactions (from lowest to highest) were: electroacupuncture (86.7%) > acupoint injection + Western medicine (84%) > acupoint injection (77.5%) > acupoint embedding (64.8%) > warm acupuncture (45.9%) > acupuncture (39.3%) > bloodletting-cupping + Western medicine (38.6%) > electroacupuncture + Western medicine (31.6%) > Western medicine (31.5%) > acupuncture + Western medicine (26.1%) > bloodletting-cupping (24%), see Figure 8 for the SUCRA ranking chart.

3.5.5. Small Sample Effect Estimation. A comparative-corrected funnel plot of pain scores for the main outcome indicators was assessed by Stata 14.2 software, see Figure 9. The results showed that the funnel plot was not fully symmetrical, suggesting that there may be some publication bias or small sample effect in the study network.

4. Discussion

Patients with PHN are often accompanied by prolonged and persistent pain, which triggers other symptoms such as anxiety, depression, and sleep disturbances [53]. Although a variety of treatment options have been proposed, first-line treatment options are still predominant in clinical practice [54], but their efficacy is not entirely reliable [8]. Acupuncture therapy based on meridian theory is widely regarded as potentially beneficial and safe for the treatment of neuropathic pain [55, 56]. The efficacy and safety of acupuncture alone or in combination with Western medicine in the treatment of PHN has been clinically proven, and the selection of the optimal combination has become the focus of current research.

This study evaluated the effects of acupuncture-related therapies alone or in combination with Western medicine on pain scores, overall effectiveness, and adverse reaction rates in patients with PHN. The results of the study showed that acupoint injection + Western medicine was superior to acupuncture, acupuncture + Western medicine, electroacupuncture, bloodletting-cupping, and Western medicine, and bloodletting-cupping + Western medicine was superior to Western medicine in terms of improving pain scores. The results of the probability ranking showed that acupoint injection + Western medicine > bloodletting-cupping > bloodletting-cupping + Western medicine > warm acupuncture > acupuncture + Western medicine > fire acupuncture > electroacupuncture + Western medicine > acupuncture > electroacupuncture > acupoint embedding + Western medicine > fire acupuncture + Western medicine > acupoint embedding > Western medicine. In terms of total efficiency, acupuncture + Western medicine was superior to bloodletting-cupping, bloodletting-cupping + Western medicine and Western medicine, acupuncture was superior to Western medicine and fire acupuncture was superior to Western medicine. The results of the probability ranking showed that acupuncture + Western medicine > bloodletting-cupping + Western medicine > acupoint embedding > fire acupuncture > acupuncture > bloodletting-cupping > electroacupuncture > acupoint embedding + Western medicine > Western medicine. In terms of adverse reaction rates, acupoint injection + Western medicine was superior to acupuncture, acupuncture + Western medicine, bloodletting-cupping and Western medicine, and acupoint embedding was superior to Western medicine and bloodletting-cupping. The results of the probability ranking showed that electroacupuncture > acupoint injection + Western medicine > acupoint injection > acupoint embedding > warm acupuncture > acupuncture > bloodletting-cupping + Western medicine > electroacupuncture + Western medicine > Western medicine > acupuncture + Western medicine > bloodletting-cupping. The analysis of the above indicators showed that Western medicine ranked low in terms of improvement in pain, overall effectiveness, and adverse reaction rate, which could be seen as a complementary and alternative option to first-line treatment options. Although the ranking of efficacy varied between indicators, the rankings of acupoint injection + Western medicine, bloodletting-cupping, bloodletting-cupping + Western medicine, and acupuncture + Western medicine were ranked at the top, and the combined results of the pain score and the ranking of the total effective rate showed that acupoint injection + Western medicine and bloodletting-cupping + Western medicine were outstanding in the treatment of PHN. Combining the results of the direct meta-analysis followed by the reticulated meta-analysis, we found no significant differences in adverse reaction rates between the treatment regimens. Considering the moderate quality of the included studies, the selection

Table 4: Results of the reticulated meta-analysis of pain scores.

I	3.23 (−0.49, 6.95)	3.77 (−0.44, 7.98)	3.86 (−0.66, 8.38)	3.97 (0.19, 7.75)	4.18 (−0.24, 8.59)	4.41 (−0.18, 9.00)	4.40 (0.35, 8.45)	4.58 (−0.98, 10.15)	4.63 (0.15, 9.12)	4.81 (−0.77, 10.38)	5.16 (−0.41, 10.74)	4.98 (0.39, 9.57)	5.50 (2.18, 8.83)
−3.23 (−6.95, 0.49)	H	0.54 (−2.54, 3.62)	0.63 (−2.86, 4.11)	0.74 (−1.70, 3.18)	0.95 (−2.20, 4.10)	1.18 (−2.40, 4.76)	1.17 (−1.53, 3.87)	1.35 (−3.41, 6.12)	1.40 (−2.01, 4.81)	1.58 (−3.21, 6.36)	1.93 (−2.85, 6.71)	1.75 (−1.83, 5.33)	2.28 (0.60, 3.95)
−3.77 (−7.98, 0.44)	−0.54 (−3.62, 2.54)	D	0.09 (−3.91, 4.09)	0.20 (−2.94, 3.35)	0.41 (−3.47, 4.29)	0.65 (−3.44, 4.73)	0.63 (−2.84, 4.10)	0.82 (−4.34, 5.97)	0.86 (−3.10, 4.83)	1.04 (−4.13, 6.21)	1.39 (−3.77, 6.56)	1.21 (−2.87, 5.29)	1.74 (−0.84, 4.32)
−3.86 (−8.38, 0.66)	−0.63 (−4.11, 2.86)	−0.09 (−4.09, 3.91)	A	0.11 (−3.43, 3.66)	0.32 (−3.89, 4.53)	0.56 (−3.84, 4.95)	0.54 (−3.29, 4.38)	0.73 (−4.68, 6.13)	0.77 (−3.51, 5.06)	0.95 (−4.47, 6.37)	1.30 (−4.11, 6.72)	1.12 (−3.28, 5.52)	1.65 (−1.42, 4.71)
−3.97 (−7.75, −0.19)	−0.74 (−3.18, 1.70)	−0.20 (−3.35, 2.94)	−0.11 (−3.66, 3.43)	C	0.20 (−3.17, 3.58)	0.44 (−3.20, 4.08)	0.43 (−2.31, 3.17)	0.61 (−4.20, 5.42)	0.66 (−2.80, 4.12)	0.83 (−3.99, 5.66)	1.19 (−3.63, 6.01)	1.01 (−2.63, 4.64)	1.53 (−0.26, 3.33)
−4.18 (−8.59, 0.24)	−0.95 (−4.10, 2.20)	−0.41 (−4.29, 3.47)	−0.32 (−4.53, 3.89)	−0.20 (−3.58, 3.17)	G	0.24 (−4.05, 4.53)	0.23 (−3.16, 3.61)	0.41 (−4.91, 5.73)	0.46 (−3.64, 4.56)	0.63 (−4.70, 5.96)	0.99 (−4.35, 6.32)	0.80 (−3.49, 5.09)	1.33 (−1.57, 4.23)
−4.41 (−9.00, 0.18)	−1.18 (−4.76, 2.40)	−0.65 (−4.73, 3.44)	−0.56 (−4.95, 3.84)	−0.44 (−4.08, 3.20)	−0.24 (−4.53, 4.05)	K	−0.01 (−3.93, 3.91)	0.17 (−5.30, 5.64)	0.22 (−4.15, 4.59)	0.39 (−5.09, 5.87)	0.75 (−4.73, 6.23)	0.56 (−3.91, 5.04)	1.09 (−2.07, 4.26)
−4.40 (−8.45, −0.35)	−1.17 (−3.87, 1.53)	−0.63 (−4.10, 2.84)	−0.54 (−4.38, 3.29)	−0.43 (−3.17, 2.31)	−0.23 (−3.61, 3.16)	0.01 (−3.91, 3.93)	E	0.18 (−4.85, 5.21)	0.23 (−3.14, 3.60)	0.40 (−4.64, 5.45)	0.76 (−4.28, 5.80)	0.58 (−3.35, 4.50)	1.10 (−1.22, 3.42)
−4.58 (−10.15, 0.98)	−1.35 (−6.12, 3.41)	−0.82 (−5.97, 4.34)	−0.73 (−6.13, 4.68)	−0.61 (−5.42, 4.20)	−0.41 (−5.73, 4.91)	−0.17 (−5.64, 5.30)	−0.18 (−5.21, 4.85)	J	0.05 (−5.33, 5.43)	0.22 (−6.10, 6.54)	0.58 (−5.74, 6.90)	0.39 (−5.08, 5.86)	0.92 (−3.54, 5.38)
−4.63 (−9.12, −0.15)	−1.40 (−4.81, 2.01)	−0.86 (−4.83, 3.10)	−0.77 (−5.06, 3.51)	−0.66 (−4.12, 2.80)	−0.46 (−4.56, 3.64)	−0.22 (−4.59, 4.15)	−0.23 (−3.60, 3.14)	−0.05 (−5.43, 5.33)	N	0.17 (−5.22, 5.57)	0.53 (−4.86, 5.92)	0.34 (−4.02, 4.71)	0.87 (−2.14, 3.88)
−4.81 (−10.38, 0.77)	−1.58 (−6.36, 3.21)	−1.04 (−6.21, 4.13)	−0.95 (−6.37, 4.47)	−0.83 (−5.66, 3.99)	−0.63 (−5.96, 4.70)	−0.39 (−5.87, 5.09)	−0.40 (−5.45, 4.64)	−0.22 (−6.54, 6.10)	−0.17 (−5.57, 5.22)	O	0.36 (−5.97, 6.69)	0.17 (−5.31, 5.65)	0.70 (−3.78, 5.18)
−5.16 (−10.74, 0.41)	−1.93 (−6.71, 2.85)	−1.39 (−6.56, 3.77)	−1.30 (−6.72, 4.11)	−1.19 (−6.01, 3.63)	−0.99 (−6.32, 4.35)	−0.75 (−6.23, 4.73)	−0.76 (−5.80, 4.28)	−0.58 (−6.90, 5.74)	−0.53 (−5.92, 4.86)	−0.36 (−6.69, 5.97)	F	−0.18 (−5.66, 5.30)	0.34 (−4.13, 4.82)
−4.98 (−9.57, −0.39)	−1.75 (−5.33, 1.83)	−1.21 (−5.29, 2.87)	−1.12 (−5.52, 3.28)	−1.01 (−4.64, 2.63)	−0.80 (−5.09, 3.49)	−0.56 (−5.04, 3.91)	−0.58 (−4.50, 3.35)	−0.39 (−5.86, 5.08)	−0.34 (−4.71, 4.02)	−0.17 (−5.65, 5.31)	0.18 (−5.30, 5.66)	L	0.53 (−2.64, 3.69)
−5.50 (−8.83, −2.18)	**−2.28 (−3.95, −0.60)**	−1.74 (−4.32, 0.84)	−1.65 (−4.71, 1.42)	−1.53 (−3.33, 0.26)	−1.33 (−4.23, 1.57)	−1.09 (−4.26, 2.07)	−1.10 (−3.42, 1.22)	−0.92 (−5.38, 3.54)	−0.87 (−3.88, 2.14)	−0.70 (−5.18, 3.78)	−0.34 (−4.82, 4.13)	−0.53 (−3.69, 2.64)	B

Notes. The above data represented the confidence interval. The bold font indicated that there was a statistically significant difference between the two treatments. A, warm acupuncture; B, Western medicine; C, acupuncture + Western medicine; D, bloodletting-cupping + Western medicine; E, acupuncture; F, fire acupuncture + Western medicine; G, fire acupuncture; H, bloodletting-cupping; I: acupoint injection + Western medicine; J, acupoint injection; K, electroacupuncture + Western medicine; L, acupoint embedding; N, electroacupuncture; O, acupoint embedding + Western medicine.

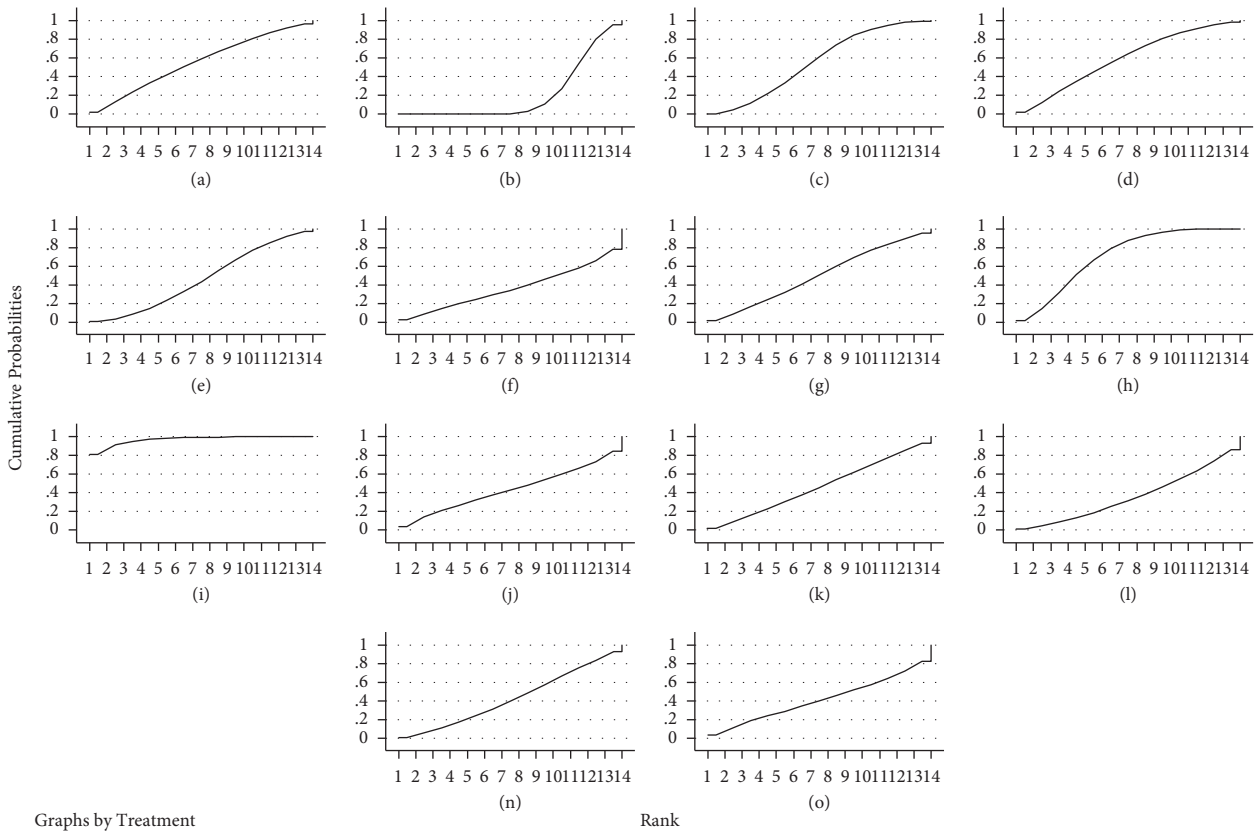

Figure 6: SUCRA ranking of pain scores for different interventions. *Notes*. In the figure, RANK is the horizontal coordinate, indicating the possible ranks, cumulative probabilities is the vertical coordinate, indicating the probability of being at this rank, and the area under the curve is used to represent the overall probability of the treatment measure.

needs to be clinically justified in relation to the characteristics of the patients' conditions, and the probability ranking results are for clinicians' reference only.

4.1. Limitations of this study. (i) Some of the studies did not specifically describe the randomisation method, allocation concealment, and blinding, which affected the efficacy of

Table 5: Results of the reticulated meta-analysis of total efficiency.

C	−0.03 (−0.43, 0.36)	−0.11 (−0.34, 0.12)	−0.13 (−0.33, 0.08)	−0.13 (−0.33, 0.08)	−0.19 (−0.37, −0.01)	−0.22 (−0.52, 0.08)	−0.25 (−0.48, −0.02)	−0.29 (−0.44, −0.14)
0.03 (−0.36, 0.43)	D	−0.08 (−0.49, 0.33)	−0.09 (−0.49, 0.30)	−0.09 (−0.49, 0.31)	−0.16 (−0.54, 0.23)	−0.19 (−0.64, 0.27)	−0.21 (−0.62, 0.19)	−0.25 (−0.62, 0.11)
0.11 (−0.12, 0.34)	0.08 (−0.33, 0.49)	L	−0.01 (−0.24, 0.21)	−0.01 (−0.24, 0.22)	−0.08 (−0.28, 0.13)	−0.11 (−0.43, 0.21)	−0.14 (−0.38, 0.11)	−0.18 (−0.35, 0.00)
0.13 (−0.08, 0.33)	0.09 (−0.30, 0.49)	0.01 (−0.21, 0.24)	G	0.00 (−0.14, 0.14)	−0.07 (−0.21, 0.08)	−0.09 (−0.36, 0.18)	−0.12 (−0.34, 0.10)	−0.16 (−0.30, −0.02)
0.13 (−0.08, 0.33)	0.09 (−0.31, 0.49)	0.01 (−0.22, 0.24)	−0.00 (−0.14, 0.14)	E	−0.07 (−0.21, 0.08)	−0.09 (−0.33, 0.14)	−0.12 (−0.35, 0.10)	−0.16 (−0.31, −0.02)
0.19 (0.01, 0.37)	0.16 (−0.23, 0.54)	0.08 (−0.13, 0.28)	0.07 (−0.08, 0.21)	0.07 (−0.08, 0.21)	H	−0.03 (−0.30, 0.24)	−0.06 (−0.26, 0.14)	−0.10 (−0.20, 0.00)
0.22 (−0.08, 0.52)	0.19 (−0.27, 0.64)	0.11 (−0.21, 0.43)	0.09 (−0.18, 0.36)	0.09 (−0.14, 0.33)	0.03 (−0.24, 0.30)	N	−0.03 (−0.35, 0.29)	−0.07 (−0.33, 0.20)
0.25 (0.02, 0.48)	0.21 (−0.19, 0.62)	0.14 (−0.11, 0.38)	0.12 (−0.10, 0.34)	0.12 (−0.10, 0.35)	0.06 (−0.14, 0.26)	0.03 (−0.29, 0.35)	O	−0.04 (−0.21, 0.13)
0.29 (0.14, 0.44)	0.25 (−0.11, 0.62)	0.18 (−0.00, 0.35)	**0.16 (0.02, 0.30)**	**0.16 (0.02, 0.31)**	0.10 (−0.00, 0.20)	0.07 (−0.20, 0.33)	0.04 (−0.13, 0.21)	B

Notes. The above data represented the confidence interval. The bold font indicated that there was a statistically significant difference between the two treatments. B, Western medicine; C, acupuncture + Western medicine; D, bloodletting-cupping + Western medicine; E, acupuncture; G, fire acupuncture; H, bloodletting-cupping; L, acupoint embedding; N, electroacupuncture; O, acupoint embedding + Western medicine.

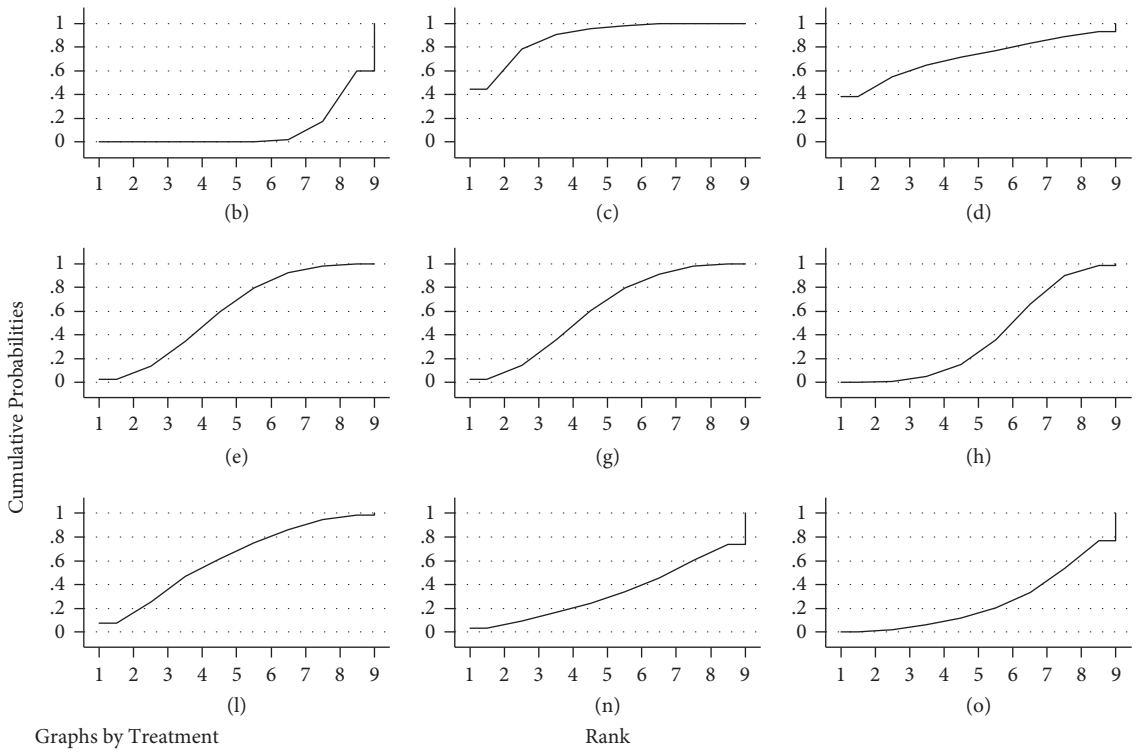

Figure 7: SUCRA ranking of the total effectiveness of different interventions. *Notes*. In the figure, RANK is the horizontal coordinate, indicating the possible ranks; cumulative probabilities is the vertical coordinate, indicating the probability of being at this rank, and the area under the curve is used to represent the overall probability of the treatment measure.

testing the results. (ii) The small sample size of the included studies may have limited the accuracy of the results of this study. (iii) The type and dosage of anti-rheumatic drugs, the selection of acupuncture points for acupuncture-related therapies, and the duration of treatment vary in the included literature, which may increase clinical heterogeneity.

Table 6: Results of the reticulated meta-analysis of adverse reactions.

N	0.97 (−2.03, 3.97)	0.52 (−3.65, 4.69)	1.69 (−1.24, 4.61)	1.97 (−1.09, 5.04)	2.12 (−0.77, 5.01)	2.11 (−0.89, 5.10)	2.25 (−0.83, 5.33)	2.20 (−0.68, 5.08)	2.34 (−0.70, 5.39)	2.25 (−0.63, 5.14)
−0.97 (−3.97, 2.03)	I	−0.45 (−3.58, 2.68)	0.71 (−0.28, 1.71)	1.00 (−0.35, 2.35)	1.15 (0.25, 2.04)	1.14 (−0.05, 2.32)	1.28 (−0.11, 2.67)	1.23 (0.37, 2.08)	1.37 (0.07, 2.68)	1.28 (0.41, 2.15)
−0.52 (−4.69, 3.65)	0.45 (−2.68, 3.58)	J	1.16 (−1.89, 4.22)	1.45 (−1.74, 4.64)	1.59 (−1.43, 4.62)	1.59 (−1.54, 4.71)	1.73 (−1.48, 4.94)	1.68 (−1.34, 4.69)	1.82 (−1.35, 5.00)	1.73 (−1.29, 4.75)
−1.69 (−4.61, 1.24)	−0.71 (−1.71, 0.28)	−1.16 (−4.22, 1.89)	L	0.29 (−0.88, 1.45)	0.43 (−0.14, 1.01)	0.42 (−0.54, 1.39)	0.56 (−0.65, 1.77)	0.51 (0.00, 1.02)	0.66 (−0.45, 1.77)	0.57 (0.03, 1.10)
−1.97 (−5.04, 1.09)	−1.00 (−2.35, 0.35)	−1.45 (−4.64, 1.74)	−0.29 (−1.45, 0.88)	A	0.14 (−0.94, 1.23)	0.14 (−1.20, 1.47)	0.28 (−1.24, 1.79)	0.22 (−0.82, 1.27)	0.37 (−1.07, 1.81)	0.28 (−0.78, 1.34)
−2.12 (−5.01, 0.77)	**−1.15 (−2.04, −0.25)**	−1.59 (−4.62, 1.43)	−0.43 (−1.01, 0.14)	−0.14 (−1.23, 0.94)	E	−0.01 (−0.88, 0.86)	0.13 (−1.00, 1.27)	0.08 (−0.19, 0.35)	0.23 (−0.80, 1.25)	0.14 (−0.19, 0.46)
−2.11 (−5.10, 0.89)	−1.14 (−2.32, 0.05)	−1.59 (−4.71, 1.54)	−0.42 (−1.39, 0.54)	−0.14 (−1.47, 1.20)	0.01 (−0.86, 0.88)	D	0.14 (−1.23, 1.51)	0.09 (−0.74, 0.91)	0.23 (−1.05, 1.52)	0.15 (−0.70, 0.99)
−2.25 (−5.33, 0.83)	−1.28 (−2.67, 0.11)	−1.73 (−4.94, 1.48)	−0.56 (−1.77, 0.65)	−0.28 (−1.79, 1.24)	−0.13 (−1.27, 1.00)	−0.14 (−1.51, 1.23)	K	−0.05 (−1.15, 1.05)	0.09 (−1.38, 1.57)	0.01 (−1.11, 1.12)
−2.20 (−5.08, 0.68)	**−1.23 (−2.08, −0.37)**	−1.68 (−4.69, 1.34)	**−0.51 (−1.02, −0.00)**	−0.22 (−1.27, 0.82)	−0.08 (−0.35, 0.19)	−0.09 (−0.91, 0.74)	0.05 (−1.05, 1.15)	B	0.15 (−0.84, 1.14)	0.06 (−0.12, 0.23)
−2.34 (−5.39, 0.70)	**−1.37 (−2.68, −0.07)**	−1.82 (−5.00, 1.35)	−0.66 (−1.77, 0.45)	−0.37 (−1.81, 1.07)	−0.23 (−1.25, 0.80)	−0.23 (−1.52, 1.05)	−0.09 (−1.57, 1.38)	−0.15 (−1.14, 0.84)	C	−0.09 (−1.09, 0.92)
−2.25 (−5.14, 0.63)	**−1.28 (−2.15, −0.41)**	−1.73 (−4.75, 1.29)	**−0.57 (−1.10, −0.03)**	−0.28 (−1.34, 0.78)	−0.14 (−0.46, 0.19)	−0.15 (−0.99, 0.70)	−0.01 (−1.12, 1.11)	−0.06 (−0.23, 0.12)	0.09 (−0.92, 1.09)	H

Notes. The above data represented the confidence interval. The bold font indicated that there was a statistically significant difference between the two treatments. A, warm acupuncture; B, Western medicine; C, acupuncture + Western medicine; D, bloodletting-cupping + Western medicine; E, acupuncture; H, bloodletting-cupping; I: acupoint injection + Western medicine; J, acupoint injection; K, electroacupuncture + Western medicine; L, acupoint embedding; N, electroacupuncture.

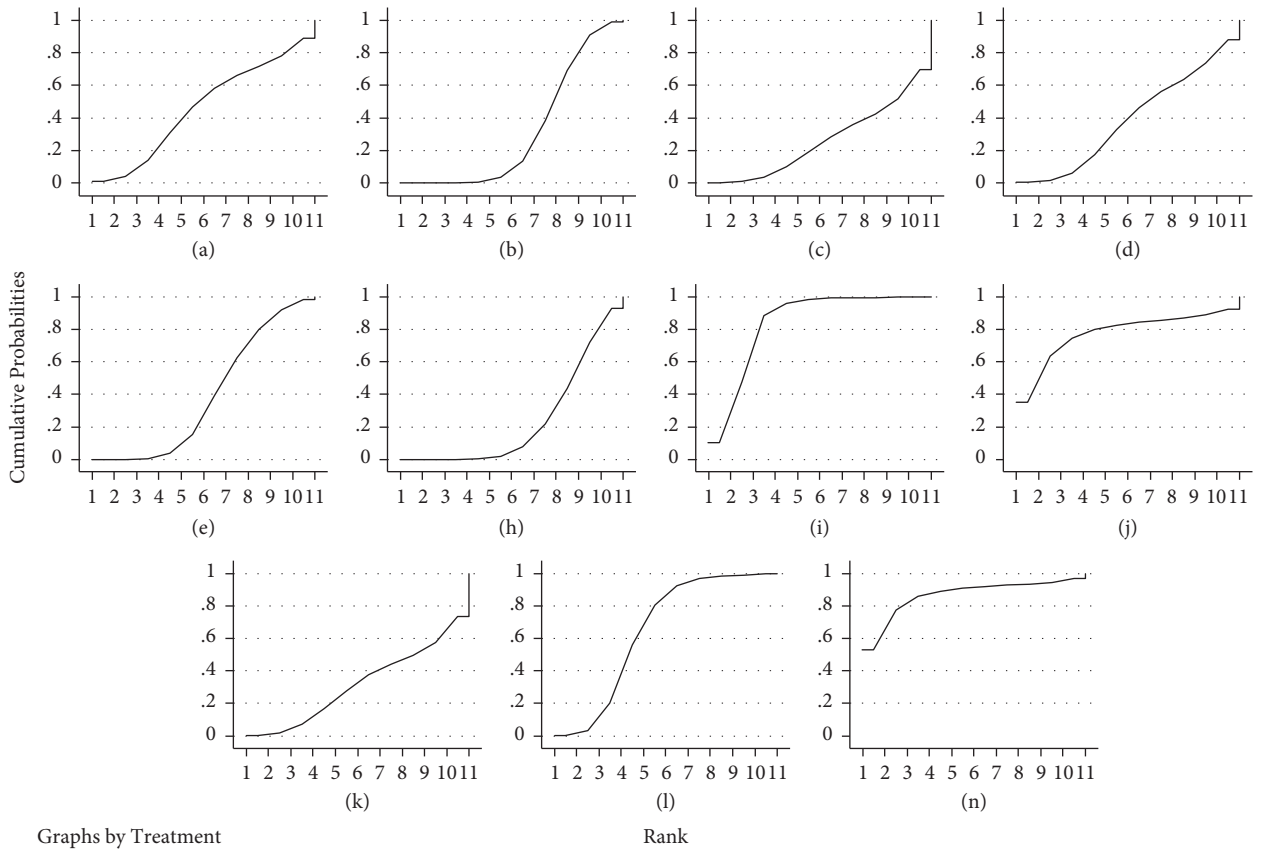

Figure 8: SUCRA ranking of rates of adverse reactions to different interventions. Notes. In the figure, RANK is the horizontal coordinate, indicating the possible ranks, cumulative probabilities is the vertical coordinate, indicating the probability of being at this rank, and the area under the curve is used to represent the overall probability of the treatment measure.

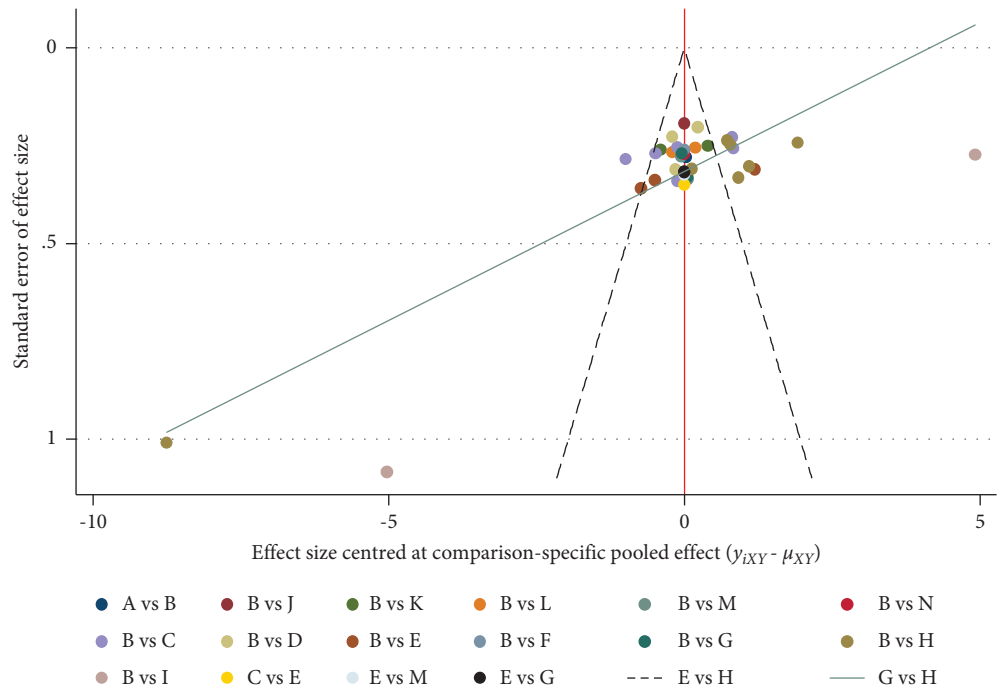

Figure 9: Comparison of pain scores-corrected funnel plot. Notes. (a) Warm acupuncture; (b) Western medicine; (c) acupuncture + Western medicine; (d) bloodletting-cupping + Western medicine; (e) acupuncture; (f) fire acupuncture + Western medicine; (g) fire acupuncture; (h) bloodletting-cupping; (i) acupoint injection + Western medicine; (j) acupoint injection; (k) electroacupuncture + Western medicine; (l) acupoint embedding; (n) electroacupuncture; (o) acupoint embedding + Western medicine.

(iv) There was some publication bias and a small sample effect in the included studies, which affects the reliability of the findings.

5. Conclusion

In summary, after a comprehensive comparison of the outcome indicators of 14 different treatment regimens, acupoint injection + Western medicine and bloodletting-cupping + Western medicine were considered to be the best combination regimens for the treatment of PHN. The appropriate treatment modality should be selected in clinical practice in the context of the actual situation. Due to the limitations of the study, the above conclusions still need to be validated by further multicentre, large-sample prospective randomised controlled clinical trials.

Abbreviations

PHN: Postherpetic neuralgia
RCTs: Randomised controlled trials
HZ: Herpes zoster
TCAs: Tricyclic antidepressants
NMA: Network meta-analysis
VAS: Visual analogue scale
CNKI: China knowledge network
SMD: Standard mean difference
RR: Relative risk
SUCRA: Surface under the cumulative ranking.

Data Availability

The data used to support the findings of this study are included with in the article and the supplementary information files.

Disclosure

Haiyan Wang and Renhong Wan are the co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Supplementary Materials

Table S1: the PRISMA checklist. Table S2: Direct comparison of meta-analysis results. Figure S1~S10: Sensitivity analysis of pain scores. Figure S11~S16: Sensitivity analysis of total efficiency. Figure S17~S19: Sensitivity analysis of adverse reactions. (*Supplementary Materials*)

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Research Article

Exploring the Feasibility of Virtually Delivered Auricular Point Acupressure in Self-Managing Chronic Pain: Qualitative Study

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Background. Chronic pain remains highly prevalent. Current pharmacological and non-pharmacological strategies have not adequately managed chronic pain which has contributed to disability and high healthcare costs. With existing challenges in providing adequate pain care and access, we tested vAPA, a virtually delivered, self-management intervention using Auricular Point Acupressure (APA) by mobile app and virtual consultations (telehealth). Our key purpose was to evaluate the feasibility of the vAPA in self-managing chronic pain in preparation for a future randomized controlled trial. *Methods*. We conducted a descriptive, qualitative study evaluating our 4-week vAPA intervention among 18 participants. We used directed qualitative content analysis. *Results and Conclusion*. Participants perceived that vAPA was feasible (acceptable, useable, practical, and beneficial). In addition, the following themes were gathered: better control of pain, less use of pain medications, self-management and motivation in pain, and expectations for pain relief. Refinements were recommended for the app, content, and delivery to improve study interventions. Findings are relevant in moving forward to a future randomized controlled trial and for wider implementation in a pragmatic clinical trial.

1. Introduction

Chronic pain is a major public health problem with increasing prevalence and is the leading cause of disability in the United States and worldwide [1–7]. Chronic pain is described as having an "unpleasant sensory and emotional experience [8]," lasting beyond usual healing time, persisting constantly for at least three months or half of the days for the past 6 months [9]. Approximately 20% of American adults suffer from chronic pain and 8% of them are highly impacted and burdened with limitations in their activities of daily living [1]. As such, chronic pain is the second most common reason for healthcare visits in the United States [5, 10], resulting in over $635 billion in medical care costs, loss of productivity related to disability, and lost wages [9]. Globally, 1 in 10 individuals suffer from chronic pain, leading to high healthcare needs, costs, and great societal burden [11].

Despite multiple pharmacotherapy and non-pharmacological modalities used to address chronic pain, inadequate management persists, contributing to the overutilization of healthcare resources with poor patient outcomes [12–14]. Pain management is an international basic human right [11] and the Institute of Medicine has recommended guidelines for non-pharmacological, self-management strategies to manage pain [9]; however, utilization of these strategies in clinical practice has been challenging and access to pain care continues to be limited [15]. The salient need for better pain management measures persists.

This study focuses on the use of Auricular Point Acupressure (APA) to assist patients in the self-management of their pain. APA is based on the principles of acupuncture which is a non-pharmacological modality supported with significant evidence in managing pain effectively, and hence has been recommended by current guidelines [15, 16].

With the Coronavirus-19 pandemic, the burden suffered by patients with chronic pain has been magnified [17] as the availability of pain treatments is limited from fewer in-person visits, thereby delaying adequate access to care [18]. Therefore, we conducted a pilot study to evaluate virtually delivered APA (vAPA). This qualitative research was done in the context of our pilot study with an overall goal to improve our intervention for a future randomized controlled trial (RCT). We were guided by the recommendations from O'Cathain and colleagues in maximizing the value of qualitative research in feasibility studies to prepare for an RCT [19]. Hence, our *overall purpose* was to *explore the feasibility of vAPA in the self-management of chronic pain.* The *overarching research question* was as follows: is vAPA feasible in self-managing chronic pain. The specific follow-up questions were related to key domains to evaluate feasibility such as perceived acceptability, usability, practicality, and benefits of vAPA [20, 21].

1.1. Background. Pharmacologic therapy such as analgesics—especially opioids—are the most common treatments used by patients for chronic pain; however, excessive and inappropriate opioid use has resulted in the current opioid epidemic [22–24]. Even other analgesics, such as nonsteroidal anti-inflammatory drugs, can potentially cause adverse effects such as renal insufficiency, gastrointestinal bleeding, hypertension, or congestive heart failure [22].

Non-pharmacologic modalities are recommended in guidelines but these have barriers to implementation, including limited access and availability, lack of insurance coverage, low reimbursement, high costs, limited capacity, and more time for required visits, among others [9, 15]. Even acupuncture, which is now included as one of the non-pharmacological modalities in pain management guidelines, has barriers to widespread implementation. Acupuncture involves complex provider assessment and individual treatment by trained providers (300 hours required for physicians or 1,800 hours of acupuncture training from an accredited school); its implementation is also limited due to labor intensity [25], inadequate insurance coverage [26, 27], a relative dearth of acupuncturists, and geographic inaccessibility [28].

Less accessibility and availability as well as the higher costs associated with certain pain treatment modalities present an excellent opportunity for APA in self-managing chronic pain. APA was derived from traditional Oriental Medicine's auricular acupuncture, developed into modern science in the 1980s by Paul Nogier, MD [29–31]. Dr. Nogier mapped a somatotopic representation of the human body onto the ear. Specific points on the ear (acupoints) correspond to specific organs and areas of the body and by stimulating these ear points, symptomatic parts of the body can be treated. For systematic diagnosis, locations of ear points corresponding to the symptomatic body part is confirmed by electrodermal responses (i.e., an electrical point finder or a small non-invasive probe) [32, 33]. Once the ear points are identified, acupuncture-like stimulations are introduced into these points, classically with the use of needles, electrically [33, 34], or with APA using pellets or Vaccaria seeds in a non-invasive manner [35]. Vaccaria seeds are natural, non-toxic botanical seeds of no medicinal value that is used in auricular acupressure. These seeds are applied to appropriate ear points; patients stimulate these ear points at least three times a day for three minutes each time, and any time during the day when they need to reduce pain. The underlying theory of auricular acupuncture posits that nerves in the outer ear correspond to specific areas of the brain, and that these areas have a reflex connection with specific parts of the body [33, 34]. The treatment of ear points can stimulate the brain to correct its pathological reflex centers [36], change levels of serum pro- and anti-inflammatory cytokines [37–40], and induce reflex reactions in the body to relieve body pathology [29, 34, 41].

Our interdisciplinary team has conducted several trials and accumulated significant evidence for chronic pain reduction using APA compared to sham APA. Our team demonstrated the following: (1) significant rapid and sustained effects on pain-related outcomes—APA resulted in rapid pain relief (≥38% three minutes post-APA [42, 43]) with >44% pain relief and >28% improved physical function at follow-up after 4 weeks of APA [35, 44–49]; (2) reduced use of pain medications—after 4 weeks of APA, ≥60% of participants reported less use of pain medications [35, 50]; (3) similar effectiveness between interventionist-administered vs. self-administered APA—we developed a self-guided, mobile-enabled APA application (app) to allow patients to self-administer APA[51]. After 4 weeks, 26 users showed an average reduction of 46% in pain intensity and 31% in pain interference [51]; and (4) successful integration of APA into a major healthcare system in real-world clinical practice [43, 52]—patients who received APA by trained nurses achieved 71% pain reduction post-48 hours of APA [43]. APA is now included in the electronic medical records of this major healthcare system in eastern US as one of the treatments for pain.

To further advance APA and prepare it for widespread dissemination—especially when in-person healthcare visits are limited—we developed and piloted our *vAPA intervention*. vAPA is a virtually delivered APA, leveraging technology using our tested mobile-enabled app featuring APA videos and supplemented with secured, remote video conferencing by Zoom. Participants received study instructions and were sent an APA kit containing a probe (used to find ear points) and seeds for placement along the ear points (about 2 mm in diameter) with pre-cut, waterproof tape used to secure the seeds (about 6 mm^2) on their specific ear points. They were also given access to our app which provided detailed instructions, ear graphic images, and steps for finding ear points specific to their pain complaint through 2 short (5 minutes each) videos. Participants were then instructed to self-administer APA to

manage their chronic pain for four weeks. During the first week of APA use, participants were advised to e-mail photographs of their ears showing their seed placements. A virtual session was scheduled individually to conduct sessions similar to telehealth and the following were performed systematically during this session: (1) review of ear photographs with ear point readjustments performed as needed especially considering current pain levels (inaccurate placement will not reduce pain), and further ear graphic images were provided to help with proper placement; (2) response to any questions from participants related to the intervention and their chronic pain; and (3) self-management support to facilitate participant capabilities and motivation to become active participants in their pain care [53, 54]. For data collection, we measured pain-related outcomes, analgesic use, and APA adherence. Time points included baseline (pre-intervention), immediate post 4-week intervention, and 1-month post completion. We then conducted interviews virtually at the last time point (1-month post completion). This manuscript describes the results of the interview findings.

In conducting this pilot study on vAPA, it was very important to conduct qualitative research to evaluate our intervention content and delivery, trial design and study processes, and outcomes. In doing so, the guidelines put forth by O'Cathain and colleagues were found useful and the best fitting to allow us to understand how our participants perceived vAPA in significant domains related to feasibility such as acceptability, usability, practicality, and perceived benefits. These were operationally defined and adapted for use in this study as follows: [20, 21] (1) *acceptability* (satisfaction, what participants like about the intervention, and their intent to continue); (2) *usability and implementation* (participant engagement and any changes or recommendations to the intervention); (3) *practicality* (cost and ability to carry out the intervention); and (4) *perceived benefits* (improvement in pain and related outcomes). These domains in evaluating feasibility were found to be the best addressed in a qualitative study [19].

Based on O'Cathain and colleagues [19, 55, 56], conducting this qualitative research allowed us to improve our planned intervention for refinement, explore possible challenges, and facilitate prospect optimization of the intervention in a future RCT. This process is important allowing for necessary changes with significant implications to inform a robust RCT. This qualitative research, therefore is placed within an evaluative framework [56, 57] for effective refinement of the vAPA.

2. Methods

2.1. Design. This is a descriptive, qualitative study focusing on the feasibility of vAPA. This qualitative research was conducted during piloting of the vAPA. We used the Consolidated Criteria for Reporting Qualitative Research checklist as a guide in reporting this study [58]. Quantitative findings were published in a separate manuscript [59]; this was submitted separately for publication due to the large amount of data gathered.

In conducting this qualitative research, we were guided by the recommended key steps from O'Cathain and colleagues: [19] (1) we identified the feasibility questions related to our pilot study for our vAPA intervention, (2) we selected the appropriate design and methods to address these questions, (3) we implemented our pilot study and conducted data collection while analyzing our qualitative data in an iterative and dynamic process, (4) we worked as a team throughout, and (5) we reported our findings, then, progressed to refining our intervention toward a future RCT for vAPA. These key steps provided clear guidance for applying qualitative research in a feasibility study prior to undertaking an RCT with the goal of improving the intervention for a full trial.

Three researchers (CY, NL, JK) conducted the interviews after conferring on the interview questions and process in order to facilitate consistency. These researchers worked with the larger team conducting the pilot study to have an adequate understanding of the overall study but independent enough so that the participants could offer honest feedback in the interview sessions. Two of these researchers are PhD-prepared faculty members and 1 is a PhD student—all with background, knowledge, and training in qualitative research.

2.2. Participants and Study Setting. Inclusion criteria were as follows: (1) 18 years or older, (2) pain that has persisted for at least 3 months or at least half of the days in the past 6 months, (3) average pain intensity ≥4 on a 11-point numerical pain scale in the previous week, (4) able to apply pressure to taped seeds on their ear points, and (5) access to a mobile device to be able to download our app and participate in our virtual session. Patients with the following were excluded: (1) malignant or autoimmune diseases, (2) known acute compression fractures, (3) use of some hearing aids that may obstruct placement of seeds on specified ear points, and (4) allergy to tape. Using purposing sampling, we received 31 referrals from healthcare providers at Johns Hopkins Medicine and 55 inquiries from individuals at different states who learned about our study from our advertisements. Fifty-six participants were excluded for various reasons (e.g., not meeting the inclusion criteria, changed their mind, unable to commit to study). Of the 30 remaining who were enrolled in this study, two dropped out because of new medical conditions unrelated to APA; one dropped out because of a very busy schedule, and two failed to schedule their post-intervention visit. Consequently, 25 participants completed this study (83% retention rate). The study setting was virtual; all research activities were completed remotely. The participants expressed a great interest given the remote nature of the study which facilitated recruitment.

2.3. Procedures. We received Institutional Review Board approval (IRB00158622) for our pilot study. Our participants completed their informed consents and emailed these to us through a secure university server. Data collection included conducting semi-structured interviews using predetermined, open-ended questions relating to the feasibility

of the vAPA. Interviews were used for data collection to better understand and explore participant experiences directed on the feasibility of the vAPA in self-managing their pain, addressing our overall study purpose. The study enrollment occurred between June and July 2020; data analyses were completed in November 2020. All authors communicated prior to the interviews to facilitate consistency in the interview guide and study processes. During these communications, the authors refined the interview guide to best reflect the overarching purpose of this qualitative research in evaluating the feasibility of the APA. The authors also communicated throughout the interview schedules as data were gathered and analyzed to further refine the questions. For example, evolving themes on having "better control of pain " and "expectations for pain relief" were consistently communicated by participants from the initial interview questions regarding perceived benefits of the vAPA so these themes were further explored with the participants moving forward. This reflects the iterative and dynamic data collection and analyses of this qualitative study resulting in the emergence of important questions and production of subsequent data.

The in-depth interviews ranged from 30 to 60 minutes and were conducted 1 month after completing the vAPA intervention. Participants were interviewed based on their availability in a private setting of their choice. Secured interviews were video-recorded remotely with audio transcription. The recordings were kept confidential and secure in a university server with log-in information required, available only to the researchers involved in this study. Transcribed data, field notes, photographs, audit trails, and all participant-related information were deidentified and stored in password-protected computers.

2.4. Data Analyses. Data analyses were conducted using a deductive approach through qualitative content analysis. Content analysis is the most appropriate for exploratory studies to obtain answers needed for the identified overarching research questions [60]. Specifically, directed qualitative content analysis was conducted because of the need for a more structured process compared to a conventional approach for exploring the feasibility of the vAPA [61]. In this directed process, key feasibility domains were used for initial coding of the data into categories. These initial codings included acceptability, usability, practicality, and benefits [20, 21]. Operational definitions for each category were described previously. In reviewing various feasibility studies as well as current practices and guidelines [20, 21], it has been recommended that acceptability [20, 21], usability [20, 21], practicality [20, 21], and benefits [20, 21] be the important, key, and consistent foci necessary in the design and implementation of feasibility studies toward evidence-based interventions.

Four researchers immersed themselves in the data with repeated review of information and field notes. To help discern patterns that were systematic, data were organized into a table matrix based on the predetermined study questions and then coded manually based on the established categories. As data analyses continued throughout the interview processes, additional categories were formulated, refining the initial coding scheme. Subsequently, emerging themes resulted with continued checking and reverse process, gathering direct quotes from participant interviews supporting emerging themes. Any differences between the authors in these directed content analysis processes were resolved through discussions, and an audit trail was documented to record coding schemes and facilitate intercoder reliability. For example, it was deemed equally important to ask about any dislikes (other than what participants liked about the intervention or acceptability) and any negative impact (apart from perceived benefits). Dislikes and negative impacts were then categorized under "*Potential Barriers*" because the feedback related to these topics was not well-fitting under the four feasibility domains (see Table 1 for sample participant responses within each category).

Transcripts of the interviews were not returned to participants but member checking was conducted at the end of each interview, summarizing information gathered for accuracy or credibility and trustworthiness. A summary of the findings was further shared with 2 participants who expressed availability for review and subsequently agreed with the findings. No additional feedback or changes were received.

Throughout the study, the researchers practiced reflexivity (e.g., jotting notes and thoughts during an interview, reflecting after an interview and during transcription and data analysis). One of the research team members is a Master of Auricular Medicine, all others were trained or well-informed about APA. These knowledge and skills facilitated participant learning of APA, particularly in finding accurate ear points. However, reflexivity was practiced by the research team to minimize introducing bias, and enhance rigor and credibility [62].

3. Results

3.1. Characteristics of Participants. Twenty-five participants enrolled in the study. Three did not respond during the intervention phase, three decided to drop out because they felt that the intervention did not work, and one did not complete the interview due to a family emergency. A total of 18 participants completed our study. This number is considered appropriate for qualitative research in feasibility studies, where 5–20 are adequate, with up to 20 being able to identify about 95% of relevant data [19]. Participants were recruited through healthcare providers and self-referrals until emerging analyses showed no new knowledge was obtained, sufficient data were achieved, and data saturation was reached.

Table 2 presents the demographic characteristics of the participants ($n = 18$) who completed the study including the post-intervention interviews. The mean age of the participants was 52.39 (SD = 18.16) with a majority older than 50 years ($n = 11$, 61%) and most of them were women ($n = 13$, 72%). Approximately 56% ($n = 10$) took prescribed pain medications and 61% ($n = 11$) took over-the-counter pain medications. Some of the participants' prescribed

Table 1: Examples of participant responses coded under each categorized domain to evaluate feasibility of the vAPA.

Acceptability (satisfaction, what participants like about intervention, intent to continue)
(i) Noninvasive, I do not need to use medication.
(ii) It's a natural remedy, holistic, and this is helping to reduce the pain.
(iii) I like that it is non-pharmacologic, no side effects.
(iv) Like tiny meditation anytime the seeds are pressed, press during the higher levels of discomfort helps bring the intensity down because it gives something to focus on. I would continue because of the mediation effect, takes mind off of the pain; and will suggest to others.
(v) I would like to continue using APA for tingling in my feet.
(vi) I might try APA with my other pains (e.g., headache, etc.)
(vii) I referred to my brother-in-law. Since he started APA, he has not used any pain killers. My sister used it for sciatica pain and it worked immediately.
**Usability and Implementation (participant engagement, recommendations)*
(i) Training videos were helpful especially first time, help as a guide to place the seeds.
(ii) Videos helpful, maybe add more information on videos for clarity on finding ear points.
(iii) I watched it a couple times to understand the process and how to locate the points.
(iv) Recommend to develop a website with these videos, tips, Q&As that anyone can access.
(v) Zoom sessions very helpful and informative in locating ear points, instructions were clear; had 2 zoom meetings, these were sufficient.
(vi) The Zoom session was very helpful, nice interaction, live responses.
(vii) Instructions and explain better in the beginning as to frequency/time for pressing, to press more frequently if needed for pain, and that this is not a cure but the best to have realistic expectations.
(viii) Pictures of ears really helped.
(ix) It might be helpful if there were more photo of the ear points.
(x) Would also be better if there is a bigger diagram of the ear, both ears.
(xi) I found that sending my ear photo and receiving feedback were helpful.
(xii) Nice to participate with social distancing.
(xiii) *Participant responses related to participant engagement as to *self-management and motivation in pain* are noted in Table 3.
Practicality (cost, ability to carry out intervention)
(i) I would recommend to others because you do not have to spend money, helps alleviate the pain wherever the pain is.
(ii) It [APA] is cost-effective.
(iii) I can find my own pressure points at any time in the comfort of my home instead of depending on having to go to the doctor.
(iv) It [APA] is easy, easy to apply treatment, seeds/tapes stayed on very well, easy to find ear points.
(v) Small seeds and tapes, not easily noticed by others. I do not have to go to therapist, the treatment is simple to use and I can use whenever I feel pain.
(vi) I did not have to go anywhere, can do it [APA] at home.
(vii) I do not have to go to doctor's office, able to do all online.
(viii) I did not have problems finding the ear points.
**Perceived Benefits*
(i) Pain went from 7 to 4 = 30 to 40% improvement, very happy with this.
(ii) If push seeds, pain go down to 1, normally have pain at 5.
(iii) Pain is constant but able to get it down with pressing the seeds; there is a change and happy with change.
(iv) You can start feeling results almost immediately.
(v) Pain seems to recur a lot on days without seeds, pain is less frequent.
(vi) Back pain is better, numbness down the leg is still a challenge.
(vii) I experienced improvement on the numbness in my toe, can walk a little bit further, and increased physical activity.
(viii) Stopped tingling feeling in feet when seeds are pressed, reoccurrence of tingling is less by pressing the seeds.
(ix) I was not into alternative medicine initially but this helps control the anxiety of getting the intense pain.
(x) It [APA] relaxes, helps with pain and stress, gets mind off pain.
(xi) When I put on the seeds for the first time, I had the best sleep in years. Has been getting good sleep since. Also noticed I am more consistent with my daily exercise because I do not wake up with pain anymore.
(xii) It [APA] helped me sleep better.
(xiii) Sleep quality is better, do not wake up with pain.
(xiv) *Participant responses related to perceived benefits as *to better control of pain*, *less use of pain medications*, and *expectations for pain relief* are noted in Table 3.
Potential Barriers
(i) Hard to find pressure point to place APA, need someone help place the seeds.
(ii) Seeds and tape fall off at times.
(ii) Tapes are irritating, itchy, and sore sometimes.
(iv) Sore after pressing but soreness goes away, would rather have soreness on the ear from APA than have pain.
(v) Nothing.

Table 2: Demographic characteristics of the participants.

Variable	*N* (SD)
Age	
Mean (SD) (range)	52.39 (18.16) (24–80)
Gender (*n*)	
Male	5
Female	13
Body mass index (SD)	
Mean (SD) (range)	27.03 (4.53) (18.40–35.20)
Race/ethnicity (*n*)*	
White	14
Black/African American	1
Others	2
Marital Status (*n*)	
Currently married/live with partner	10
Divorced	3
Widowed	1
Never married	4
Employment Situation (*n*)	
Working (full time)	8
Not employed	8
On leave	2
Education level (*n*)	
High school	1
Technical or vocational school	1
College	11
Graduate	5
Estimated income before taxes (*n*)	
$20,000 to $39,999	3
$40,000 to $59,000	3
$60,000 to $100,000	7
More than $100,000	5
Current prescribed pain medication	
Yes	10
No	8
Current prescribed sleep medication	
Yes	3
No	15
Current over the counter pain medication	
Yes	11
No	7
Current over the counter sleep medication	
Yes	1
No	17

*n varied due to missing data, SD = standard deviation.

medications commonly included opioids, adjuvant analgesics, and other agents including neuropathic medications, muscle relaxants, nonsteroidal anti-inflammatory agents (prescription dose), sleep aids, and benzodiazepines.

3.2. Major Themes. Based on the coding of our participant data with sample information in Table 1, we derived five themes: the overall major theme was that the *vAPA was feasible*. Other themes were: *better control of pain, less use of pain medications, self-management and motivation in pain, and expectations for pain relief* (see Table 3).

3.2.1. vAPA Is Feasible. Based on participant responses, the overall major theme obtained was that vAPA is feasible. Several participant responses were noted in Table 1 that reflect acceptability, usability, practicality, and perceived benefits of the vAPA. Further, one participant stated overall, "the program is well organized and the staff members are helpful. " Another participant stated, "I believe your team is doing a fantastic job in helping selflessly, by teaching and coaching patients this valuable technique. Thank you and keep up your altruistic work. " There were also potential barriers particularly in initially locating ear points. Although all participants were able to successfully locate ear points accurately, two had initial challenges that were assisted with an additional virtual session, ear photos, and ear graphics pointing to precise locations. Participant responses on barriers to the treatment will serve to help improve the intervention. Importantly, no side effects nor adverse effects were noted.

3.2.2. Better Control of Pain. It is clear that the participants perceived benefits from the intervention. For instance, the benefits included, among others, pain relief or reduction, improved sleep, reduced anxiety, and that the APA had meditative effects. Pain relief also appeared to include improvement of neuropathic symptoms such as tingling and numbness. Apart from these perceived benefits and specific to this theme, participants mentioned "control of pain" that they experienced with the APA as a highly recurring experience. The intervention was something they felt they could implement any time they were in pain and consequently felt reduced pain levels based on greater control over the treatment. One participant stated, "I like the fact that I feel I am in control of managing my pain. " Another participant realized after the virtual session that he could press his ear points more frequently anytime he needed it for pain reduction. This feature of APA was reinforced during his virtual session, which resulted in better control of his pain.

3.2.3. Less Use of Pain Medications. Because the participants experienced pain relief or reduction from the intervention, they consequently used their analgesics with less frequency. This is significant because the majority of the participants took pain medications, both prescribed and over-the-counter. Others who used some natural remedies or non-pharmacological modalities also needed less of these after incorporating APA. One participant mentioned that she did not need to go and seek pain relief from a healthcare provider during the study.

3.2.4. Self-Management and Motivation in Pain. Many participants felt that personal motivation was important in being able to self-manage their pain. For example, if they actually used the APA to help with their pain, participated in the intervention, the experience of pain relief motivated them to continue further in using APA to self-manage their pain. One participant quoted a saying, "You get what you inspect, not what you expect. " To achieve the best results in pain relief, participants were motivated to

Table 3: Examples of participant responses reflecting study themes.

**vAPA is feasible*
(i) *Several participant sample responses are reflected in Table 1 reflecting acceptability, usability, practicality, and perceived benefits.
Better control of pain
(i) Being able to press the seeds when pain recurs is very convenient for me, because I can easily take care of my pain even when I am working without having to stop and take medication. I feel that it helps me stay positive and confident that I can manage my own pain without having to rely on meds.
(ii) Feel better control over pain especially when overdoing and gets a lot of pain, I press the seeds and get relief especially when pain is aggravated.
(iii) Better control, can press [ear points] anytime.
(iv) Have more control of pain, press the seeds when in pain and pain improves.
(v) Feel better control over pain though just realized recently that can press more if needed for pain, able to get it down with pressing the seeds.
(vi) Better control of tingling by pressing points.
(vii) Wake up from pain then press the seeds and then able to fall asleep.
Less use of pain medications
(i) I am using less pain medication. Usually takes aspirin, tramadol and muscle relaxant as needed. Only needed to take 1 muscle relaxant during the trial.
(ii) I still use tylenol but less.
(iii) Used to take ibuprofen but has not used any at all since APA.
(iv) Needed less ibuprofen.
(v) Most of the time I have not needed to take any pain medication.
(vi) Don't usually take meds but took tylenol 3000 mg in the past and ice packs, have not had to do these.
(vii) Reduced use of pain medications like ibuprofen, lidocaine, and less use of other natural remedies like CBD oil, massage, epsom salts.
(viii) Has not been to a provider for pain.
Self-management and motivation in pain
(i) Self-motivation is important, pain should be enough motivation, do not see anything else that could be done better to motivate [to do APA].
(ii) Motivation is a personal thing; the seeds have a positive effect.
(iii) I believe this treatment is self-motivating if the patient has faith in it and finds that it helps.
(iv) Pain relief was motivation enough.
(v) This is a really good way not to use drugs.
(vi) Since I am trying to avoid using pain medication and my pain comes and goes, the treatment is an alternative choice to manage my pain.
(vii) To avoid surgery, I can use APA to manage pain.
Expectations for pain relief
(i) Expect to get pain down to 3 or 4 from 8, she was getting this pain relief with the APA.
(ii) Pain is 4-5 average, do not want to be on the medication forever so this [APA] keeps mind off it; even a decrease to 2-3 pain is ok.
(iii) 1 point drop is ok, immediate effect is better but realistic that it will take a while.
(iv) Just a decrease of 1-2 points help, takes the edge off when seeds are pressed, couple hours relief and takes a little time for pain relief, about 15–30 minutes.
(v) Pain down to 2 and 3 is ok. Current average pain is 3–5 and if goes down to 2-3, this is my minimal expectation and this is being met.
(vi) Any program that helps the pain is good.

self-manage their pain, gave themselves the opportunity to try something new and different such as APA, engaged with the intervention, and subsequently experienced pain relief.

3.2.5. Expectations for Pain Relief. Many participants were realistic about their expectations of pain relief. Even during instances when their pain did not reach zero, many participants were delighted that the APA treatment provided pain reduction, regardless of the amount of relief. Some were happy with a single point reduction of pain from their usual pain level on a scale of 0 to 10. Others were pleasantly surprised with the amount of significant pain relief they received, experiencing a substantial drop in their pain level. For example, a participant felt that her expectations for pain relief were met with her well-diminished pain so she "did not have to take pain killers around the clock" because APA significantly decreased her pain level.

4. Discussion

The qualitative approach conducted in this study is appropriate in feasibility and pilot studies and highly relevant for informing the research team, facilitating necessary changes toward improving the intervention prior to the conduct of an RCT [19]. Given all participant responses with examples noted in Table 1, we found that vAPA was feasible as a self-management tool for managing chronic pain. Participants found the intervention to be acceptable, useable, practical, and beneficial for their chronic pain and other related symptoms (e.g., numbness, tingling, anxiety, lack of sleep). Proceeding with an RCT would be the next logical step.

Exploring other participant themes, we also found that vAPA resulted in better control of chronic pain with easy access to this intervention whenever the need arises. Consequently, participants used fewer pain medications. This highlights an important potential future application of APA directed to decreasing unnecessary healthcare utilization and positively reducing current exorbitant healthcare costs associated with chronic pain [9]. Self-management of pain was also another important theme and key motivating factor for the participants to continue using APA. Self-management can influence the sustainability of APA for future use; patients implement interventions that are not only accessible but also interventions that they find beneficial, useful, and have immediate positive impact. In effect, patients become motivated and assume a more active role in self-managing their pain. It has been well documented that patients with chronic pain who actively engage in their own treatment achieve superior outcomes compared to those who take a passive approach [63, 64]. We also found that although there was some variability as to participants' pain relief expectations, many felt that even a single point drop in their usual pain level was valuable. This represents a significant finding for an intervention that is easily accessible and works immediately. Method triangulation [65] was performed to evaluate consistency of findings and enhance validity. Our quantitative findings [59] also showed reduced pain intensity among our participants.

In evaluating vAPA and assessing its ability to be scaled-up for widespread implementation and further testing, identifying potential barriers was necessary. These provided key opportunities and lessons learned for future studies to help address these barriers. For example, to assist in accurately locating ear points and securing the seeds, future intervention refinement will include the following: shorter, succinct, but additional graphic videos specific to each area of body pain with larger diagrams, larger fonts, closed captioning, and detailed instructions for better understanding and clearer demonstration of APA while maximizing its use as a self-guided tool to manage pain. The videos will reinforce the use of APA by recommending that patients press on the ear points anytime that pain recurs. This would be in addition to the minimum recommended APA practice of three times a day for three minutes each time. Additional virtual sessions may be necessary to address any questions and some may need another person to help secure the seeds to the proper ear point and minimize the seeds from falling off. We also found that some participants complained about the soreness on their ear points with the APA. There is ear soreness related to APA treatment because identifying the appropriate ear acupoints (site for acupressure stimulation) produces some initial discomfort. However, this soreness gradually disappears when body pain intensity improves [32, 66]. Thus, it is important to advise participants about this potential discomfort when they first receive APA treatment. Additionally, some participants experienced itching due to the tapes used to adhere the seeds to the ear points, indicating potential sensitivity or allergy to the tapes. Thus, a better adherent (i.e., non-allergenic tapes) should be used in future studies.

Additional refinements based on participant feedback include developing a website with educational videos including tips and Q & As, making the APA app web-enabled for easy viewing and accessibility on a computer or tablet, and using a skills checklist as a self-evaluation tool to ensure that all APA procedural steps are completed for the best results. These refinements will aid in facilitating adequate access to effective pain interventions even beyond the current pandemic given the existing challenges in accessing pain treatments and prevailing pain care disparities [67–69].

4.1. Implications. Significant implications related to the refinement of the vAPA intervention were discussed. Other important implications pertain to study recruitment and retention. Recruitment in this study was facilitated by its virtual delivery and retention was not difficult especially due to participant's perceived benefits from vAPA. Further strategies could include use of motivationally tailored messages to promote adherence, an individualized dashboard with each participant's own study outcomes for self-monitoring, participant video vignettes and discussion board to allow for networking and social engagement, and study newsletters to keep participants well-informed throughout the study. These enhancements are all important moving forward to an RCT and larger implementation by means of a pragmatic clinical trial.

The implications of this study can also lead to increasing training of APA among healthcare providers, community partners, interested patients, and other individuals for broader application to the general population. Education on the value of non-pharmacological, self-managed interventions among various stakeholders can help facilitate a significant paradigm shift in pain management interventions that are useful and less costly. Policy implications are important toward eventually covering APA in health insurances for better access to pain control for all patients with chronic pain and help address pain care disparities.

5. Limitations

This qualitative study highlighted the feasibility of vAPA which is important toward evaluating its utility toward a future RCT and further testing in a larger population of patients. However, there were limitations. Purposive sampling limits representativeness but the virtual nature of this study allowed us to recruit with a wider reach. In conducting the interviews, although the actual transcripts were not returned to the participants, member checking was conducted and a summary of the study results was shared to facilitate credibility of findings and trustworthiness. Other types of triangulations were not performed (e.g., investigator, theory, data source) [65] but method triangulation was done particularly in the area of pain relief.

6. Conclusions

This study emphasizes the importance of conducting qualitative research at the pre-RCT stage [19, 55, 56] to improve study intervention processes and help produce

the best evidence for subsequent treatment and trials. We were able to evaluate our intervention content and delivery, trial design and conduct, study processes, and outcomes all aimed at improvement and refinement of future studies.

We found that vAPA was a feasible and effective self-management tool, allowing participants to assume an active role in their own pain management and allowing them to re-establish control over their pain. With a greater sense of control over pain, participants were further motivated to continue using APA to self-manage their pain. APA has a significant potential for providing a valuable public impact in decreasing the pain epidemic, opioid crisis, and healthcare utilization and costs.

Data Availability

Data are available on request.

Disclosure

The manuscript was presented as a scientific meeting abstract at the 2021 American Society for Pain Management Nursing Conference. Funders played no role in the preparation, writing, or submission of this paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Acupuncture Analgesia in Patients with Postoperative Neck Pain: A Protocol for Systematic Review and Meta-Analysis

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Background. There is a yearly increase in pain after neck surgery, which is accompanied by high consumption of opioids. However, the opioid addiction epidemic is one of the most serious public health problems worldwide. Therefore, it is important to find suitable alternatives for opioids. Acupuncture therapy has been found effective for some types of pain control. This protocol aims to evaluate the efficacy and safety of acupuncture therapy in the treatment of pain after neck surgery. *Methods and Analysis*. We will search eight electronic databases from their inception to April 2022. Only randomized controlled trials (RCTs) using manual acupuncture, auricular acupuncture, or electroacupuncture as major therapy will be included, regardless of whether the study was published in Chinese or English. The selection of studies and data extraction will be independently completed by at least two experienced reviewers with a master's degree. The methodological quality of the included studies will be assessed by the Cochrane risk-of-bias tool. For the meta-analysis, Review Manager Statistical (RevMan V.5.3) software will be used. The results will be presented as the risk ratio (RR) for the binary data and the mean difference (MD) or standardized mean difference (SMD) for the continuous data. *Ethics and Dissemination*. This protocol for a systematic review will be submitted to a peer-reviewed journal for publication and presented at a relevant conference, and there is no need to obtain formal ethical approval. *Trial Registration Number*. PROSPERO registration number CRD42021281722.

1. Introduction

Adequate postoperative pain management is important for successful recovery and rehabilitation after surgery [1]. Neck surgery mainly involves tonsillectomy, thyroidectomy, or parathyroidectomy, and neck dissection. Depending on the type of surgical intervention, 25%–65% of patients have moderate to severe postdischarge pain, leading to their dissatisfaction with postoperative care [2]. Tonsillectomy is one of the most common surgical procedures. Each year, 500,000 individuals in the United States undergo tonsillectomy [3], which is often performed during the daytime in an ambulatory setting by otolaryngologists and pediatricians [4]. Although the *French Oto-Rhino-Laryngology Head and Neck Surgery Society* [5] and other researchers [6] have published guidelines for post-tonsillectomy pain management in adults and children, respectively, pain management remains challenging and poorly managed in clinical practice [7]. Postoperative pain after tonsillectomy is related to the indications and surgical techniques [8]. In adults, pain is always undertreated, and the type of surgery requires dissection with coagulation, which leads to severe pain [9]. In children, the most common issue is low parent and child adherence, and about 60% of children receive less medication during postoperative days than prescribed [10]. Therefore, complementary and alternative medicine (CAM) is needed to manage their pain.

In the United States, approximately 20,000 thyroidectomies and parathyroidectomies are performed each year [11, 12]. Every year, the total burden of new head and neck

cancers exceeds 10,000 new cases [13]. Opioid analgesics are the most common prescription medications used to treat postoperative pain by the surgical team. However, they may result in opioid addiction [14]. Considering the continuous increase in the number of patients, better postoperative pain management is required.

Neck dissection includes the removal of lymph nodes from the neck [15] and remains the key component of the management of neck tumors [16]. In addition to lymph node removal, it also often involves the excision of the accessory nerve (CN XI), sternocleidomastoid muscle, and internal jugular vein. Therefore, neck dissection not only leads to neck dysfunction but also to neck pain [17]. Around 30% to 70% of patients may even experience variable degrees of shoulder pain [18–20]. Hence, their quality of life is substantially affected. Although physical therapy exercises and anti-inflammatory drugs are widely used to relieve the pain after neck dissection, their efficacy is often disappointing.

An increasing number of recent studies have focused on the use of acupuncture to treat postoperative pain after tonsillectomy, thyroidectomy or parathyroidectomy, and neck dissection. The positive effects of acupuncture therapy have been mentioned in acute postoperative pain management [21]; however, there is still relatively limited progress in therapeutics for effective symptom control. Although several systematic reviews of acupuncture for postoperative pain were published from 2015 to 2020 [22–25], there is still a lack of systematic reviews and meta-analyses of acupuncture for the treatment of pain after neck surgery. Therefore, a protocol for comprehensive research on pain management is of high priority. Moreover, few studies have revealed differences in efficacy between the acupuncture therapy and the conventional treatment of postoperative neck pain.

1.1. Description of the Intervention. Acupuncture therapy is an important part of physiotherapy and has a long history in China. It is based on the concept of vital energy. The United States Food and Drug Administration (FDA) approved acupuncture needles as a medical device in 1996 [26]. Acupuncture has been suggested for some postoperative symptoms by the National Institutes of Health (NIH) [27]. As time goes by, the types of acupuncture therapy have gradually increased, and a large number of acupuncture methods are accepted in clinics, such as manual acupuncture (MA), auricular acupuncture (AA), and electroacupuncture (EA). Acupuncture therapy is effective for a variety of painful conditions [28]. Furthermore, it can be used in the perioperative period, and it exerts its effects at three different levels including the peripheral site, the spinal cord, and supraspinal structures [29]. Therefore, a more specific type of pain needs further study, and the most effective acupuncture method needs to be determined.

2. Materials and Methods

We used the PRISMA-P checklist when writing our report (PRISMA-P) [30]. The review will be conducted as per the PRISMA statement guidelines [31]. The protocol we have registered at PROSPERO is available on the website at https://www.crd.york.ac.uk/prospero/.

2.1. Types of Studies. We will search for relevant randomized controlled trials (RCTs) published from the inception date of the databases to April 2022, without any regional limitations. Both articles published in English and Chinese will be considered. Only RCTs will be included, whereas animal studies, meeting abstracts, case reports, case series, editorials, protocols, and comments will be excluded.

2.2. Types of Participants. The population of interest consists of adult patients (aged more than 18 years old) who underwent postoperative neck pain after tonsillectomy, thyroidectomy, or parathyroidectomy, or neck dissection. All eligible participants will be included regardless of age, race, gender, ethnic background, nationality, economic status, and source of cases.

2.3. Types of Intervention. We will restrict our focus to studies that used different methods of acupuncture treatment as a primary intervention. The following types of acupuncture methods will be eligible: (1) manual acupuncture (MA), which is a part of traditional Chinese medicine; in MA, pain is alleviated by inserting the needles into specific points of the body, and the mechanism seems to involve the central nervous system; (2) auricular acupuncture (AA), which mainly stimulates the acupoints of the ear and relieves pain with the pressure of the Vaccaria seeds; and (3) electroacupuncture (EA), which has been further developed based on the traditional acupuncture theory; its function is a transformation of energy. Any combination of these acupuncture types will also be included. The duration of the study research will not be restricted in our meta-analysis. However, other irrelevant needle stimulation of acupoints, such as cupping, laser acupuncture, or acupotomy, will not be considered.

2.4. Types of Comparator(s)/Control. We will evaluate the following comparisons:

(1) Acupuncture versus standard care (standard postoperative analgesic treatment)

(2) Auricular acupuncture with stickers versus stickers alone, or versus without receiving adhesive tapes or stickers

(3) Acupuncture versus placebo or sham acupuncture

We will exclude trials including combination therapy.

2.5. Types of Outcome Measures

2.5.1. Primary Outcomes. The main goal of this study is to evaluate the efficacy of different acupuncture methods and find the best treatment time. Therefore, levels of pain intensity will be an important factor, and the primary outcome

Table 1: Search strategy used in PubMed database.

Number	Search terms
1	MeSH descriptor: [neck dissection] explode all trees
2	(Tonsillectom*):ab,ti, kw or (thyroidectom*):ab,ti, kw or (parathyroidectom*):ab,ti,kw
3	1 or 2
4	MeSH descriptor: [pain, postoperative] explode all trees
5	(Postsurgical pain):ab,ti, kw or (postoperative pain)ab,ti, kw or (perioperative period):ab,ti,kw
6	4 or 5
7	MeSH descriptor: [hyperalgesia] explode all trees
8	(Hyperalg*):ab,ti, kw or (hyperalgesic sensation*):ab,ti, kw or (secondary hyperalg*):ab,ti, kw or (hyperalgesia*, thermal):ab,ti, kw or (primary hyperalgia*):ab,ti, kw or (mechanical hyperalg*):ab,ti, kw or (allodynia, thermal):ab,ti, kw or (allodynia*):ab,ti, kw or (tactile allodynia):ab,ti, kw or (mechanical allodynia):ab,ti,kw
9	7 or 8
10	6 or 9
11	MeSH descriptor: [acupuncture therapy] explode all trees
12	(Acupuncture treatment*):ab.ti.kw or (pharmacoacupuncture treatment):ab,ti, kw or (pharmacoacupuncture Therapy):ab,ti, kw or (acupotom*):ab,ti,kw
13	11 or 12
14	MeSH descriptor: [acupuncture, ear] explode all trees
15	(Ear acupuncture*):ab,ti, kw or (auricular acupuncture*):ab,ti,kw
16	14 or 15
17	MeSH descriptor: [electroacupuncture] explode all trees
18	13 or 16 or 17
19	3 and 10 and 18

indicators will include the visual analog scale (VAS) [32] or the Constant–Murley score (CMS) [33], a composite score of pain.

2.5.2. Secondary Outcomes. Secondary outcomes will include the following:

(1) The Neck Dissection Impairment Index (NDII)

(2) Numerical Rating Scale of Pain (NRS)

(3) Modified Constant–Murley score

(4) McGill Pain Questionnaire on postoperative days

(5) Incidence of vomiting, nausea, and agitation

2.6. Search Strategy

2.6.1. Electronic Search. Four English-language databases (PubMed, Embase, Web of Science, and Cochrane) and four Chinese-language databases (China National Knowledge Infrastructure, CBM, VIP Database for Chinese Technical Periodicals, and WANFANG) will be searched for RCTs published from the database's inception up to April 2022.

The search strategy will consist of three components: clinical condition (neck-dissection, tonsillectomy, thyroid, and parathyroid surgery); postoperative condition (postoperative pain, hyperalgesia, and allodynia); and intervention (manual acupuncture, electroacupuncture, and auricular acupuncture). We will use a combination of related terms and subject headings to retrieve relevant studies. The search strategy for the PubMed database is shown in Table 1.

2.6.2. Searching Other Resources. We will also search electronically the World Health Organization (WHO) International Clinical Trial Registry Platform, the National Institute of Health (NIH) clinical registry Clinical Trials, the Chinese clinical registry, and the Australian New Zealand Clinical Trials Registry. The selected studies will be screened. Moreover, grey literature (not formally published by commercial or academic publishers) will be manually searched [34]. For ongoing or unpublished RCTs, we will contact the author of the trial to obtain the latest clinical data. In addition, we will consult the experts for some potential studies and unavailable clinical data.

2.7. Data Collection and Analysis

2.7.1. Selection of Studies. First, one reviewer will use the software (EndNote X9) to import the search results and filter out the repetitive articles according to the designated strategies. Then, all of the extracted articles will be screened independently by two reviewers (JC and CD), who will examine the title, abstract, and keywords after professional training. If there are any disagreements, a third person (TL) will arbitrate. The potentially eligible full-text articles will be downloaded and screened by two reviewers (JC and CD). Later, EndNote X9 will be used again for the management of articles. When an article is excluded, the detailed reason will be recorded. The literature selection procedure is shown in Figure 1.

2.7.2. Data Extraction and Management. When the search procedure is completed, two authors (RL and SL) will independently make pilot-tested data forms to complete the screening procedure. First, duplicate literature will be excluded. Second, according to the content of the title, abstract, and full text, the compliant studies will be retained. The following information will be recorded: (1)

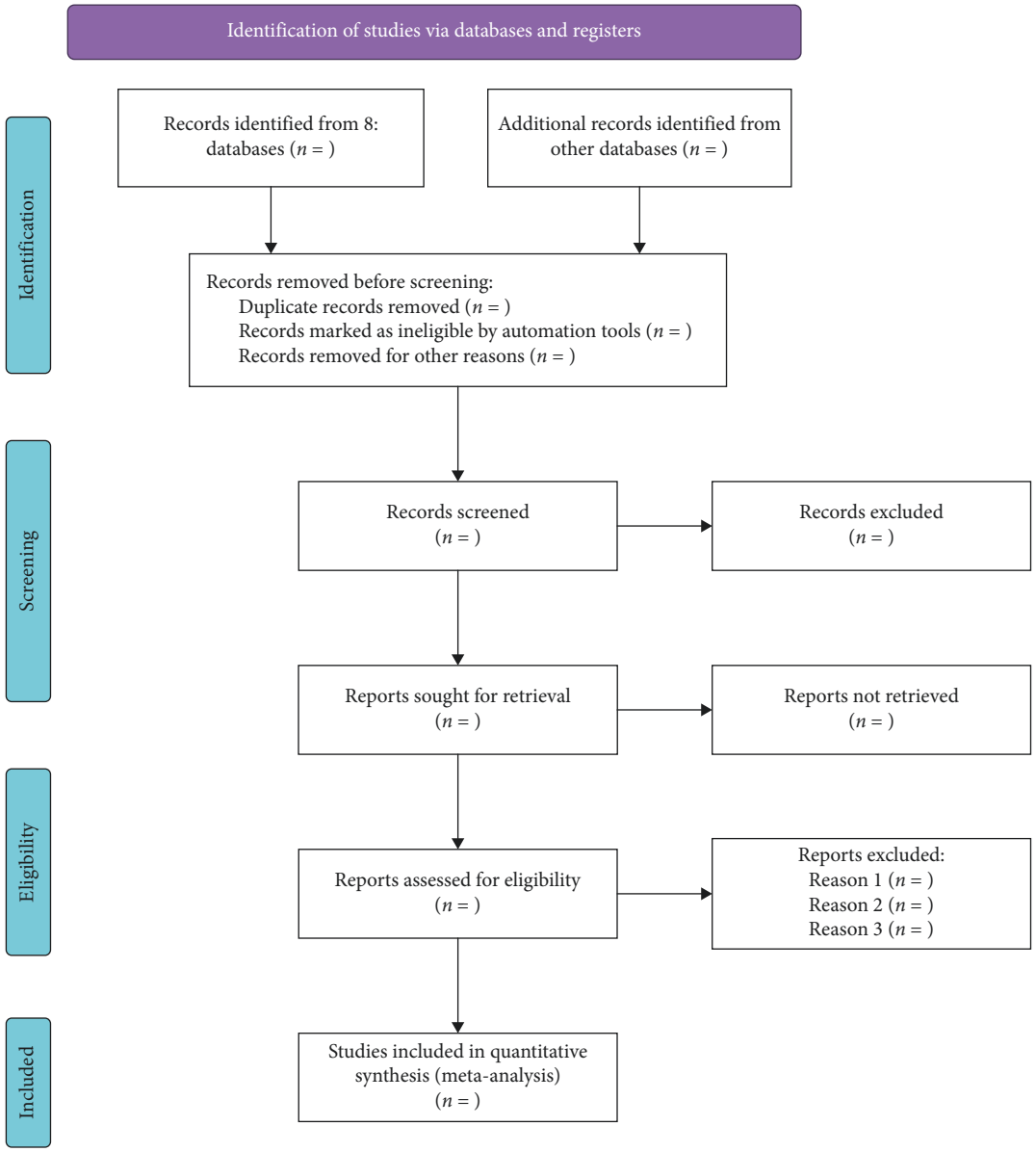

Figure 1: PRISMA 2020 flow diagram for a new systematic review and meta-analysis, which includes a search of databases and registers only.

general information (title, the first author's name, nationality, year of publication, and journal name); (2) study design (random sequence generation, allocation concealment method, blinding method, conflict of interest, sex ratio of treatment group, sex ratio of control group, age of treatment group, age of control group, and sample size); (3) intervention and comparator (type of acupuncture therapy, acupoints selection, stimulation duration, needle depths and frequency, treatment duration, follow-up duration, and details of the control group); (4) outcomes (different types of outcomes and related statistical results); (5) patients' adverse reactions; and (6) funding. In the case of insufficient available data, information will be obtained by contacting the authors or by calculations based on our previous research. If any discrepancy happens, a third reviewer (CD) will make an adjudication.

2.8. Assessment of Risk of Bias. To assess the risk of bias, we will use the Cochrane Collaboration risk-of-bias tool appraised by two reviewers [35]. The risk of bias in sequence generation involves random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, selective outcome reporting, and incomplete outcome data. Each domain will be categorized into the following three levels: low risk, unclear risk, and high risk. Any disagreement between the two reviewers will be resolved by the third reviewer (TL) through discussion.

2.9. Measures of Treatment Effect. The RevMan software V.5.3 will be used for efficacy data, including data synthesized and statistically analyzed. As an efficacy index of continuous variables, we will use the mean difference (MD)

and SMD with 95% CIs. For categorical variables, we will use the risk ratio (RR) with 95% CIs for calculation.

2.10. Dealing with Missing Data. To acquire insufficient details and missing data for the selected articles, the corresponding authors or relevant authors of the articles will be contacted. If we do not receive a response and the required data are still unobtainable, imputation will not be performed for the missing data. To avoid additional bias introduction, we will only analyze the available data.

2.11. Assessment of Heterogeneity. The assessment of clinical and methodological heterogeneity will mainly focus on the characteristics of patients, interventions, and kinds of outcomes, and it will make a comparison of the goodness of fit between the fixed-effects model and the random-effects model. The I^2 statistic, which derives from the X^2 test, will be used to assess heterogeneity across the studies according to the Cochrane Handbook for Systematic Reviews of Interventions. If $I^2 < 50\%$ and $p > 0.1$, the heterogeneity tests will show little or no statistical heterogeneity, and a fixed-effects model will be considered. In contrast, if $I^2 > 50\%$ and $p < 0.1$, the heterogeneity tests will indicate high heterogeneity, and the random-effects model will be adopted. Specifically, much more attention should be paid to the source of heterogeneity if $I^2 \geq 75\%$. Moreover, to explore the possible causes of heterogeneity, a subgroup analysis or meta-regression will be performed based on clinical characteristics.

2.12. Reporting Bias Assessment. To make sure that the results of the study are credible, reporting bias assessment will be necessary. If more than 10 trials are included [36], Begg's and Egger's tests will be used to assess the symmetry of the funnel plot by the Stata V.14.0 software.

2.13. Data Synthesis. We will use the Review Manager V.5.3 to conduct data processing from the Cochrane Collaboration. If there is little or no heterogeneity among the trials, the fixed-effects model will be used. In contrast, the random-effects model will be used for data synthesis if significant heterogeneity is shown ($I^2 \geq 50\%$). Subgroup analysis will be carefully considered if necessary. Although a descriptive analysis will be provided, we will not conduct a meta-analysis if the heterogeneity is too large [37].

2.14. Subgroup and Sensitivity Analysis. In this study, subgroup analyses will be performed based on the treatment duration, follow-up time points, surgery types, acupoint selection, or different acupuncture methods. However, the ultimate grouping will be determined depending on the inclusion of studies providing relevant data. To make sure that the conclusions are credible, we will conduct a sensitivity analysis to verify the stability and reliability of the primary outcome in terms of the following three aspects: sample size, missing data, and statistical model.

2.15. Summary of Evidence. We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to summarize the meta-analysis and grade the strength of evidence [35]. The GRADE Profiler evaluates the quality of evidence (risk of bias, heterogeneity, inconsistency, indirectness, imprecision, and publication bias), and the level will be rated as "high," "moderate," "low," or "very low" [38].

3. Discussion

With the development of society, people are generally under a state of high pressure, which leads to some serious mood-related diseases such as tonsillitis, thyroid cancer, and neck neoplasms. For treating these diseases, there are few options besides surgery. Furthermore, most doctors and nurses pay much attention to the operation period rather than to postoperative pain management. The postoperative neck pain may not only cause patients' suffering but may also lead to an addiction to opioids. Many studies have shown that acupuncture therapy is effective for postoperative neck pain [39–42] and that it may replace opioids for postoperative analgesia. However, the treatment duration, the choice of acupoints, and even the pain rating scale are quite different. Furthermore, there are currently no systematic reviews on this topic. This meta-analysis will make a comparison between different types of acupuncture and objectively infer their efficacy. Thus, this study may offer a basis for replacing opioids for postoperative neck pain management and provide a novel regime for acupuncture practice.

Although there have been some meta-studies on acupuncture for pain after tonsillectomy [43–46], a relatively strict and scientific protocol design for such a study on the comprehensive assessment of acupuncture for postoperative neck pain has not been reported yet and needs to be prioritized. The results of this study will offer doctors and patients more available options. Data collection and management will be independently conducted by more than two trained researchers to ensure the objectivity of the study. However, there will be some limitations, considering that our proposed methodology will mainly focus on the stimulation of acupoints by needles, while we will place less emphasis on the associated selection of acupoints and different ways to stimulate the acupoints. In summary, this protocol will be updated in the future if needed, and the details of the changes will be added as a supplement.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Renming Liu and Songming Li contributed equally to the manuscript.

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Review Article

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

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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 zoster-

associated 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)

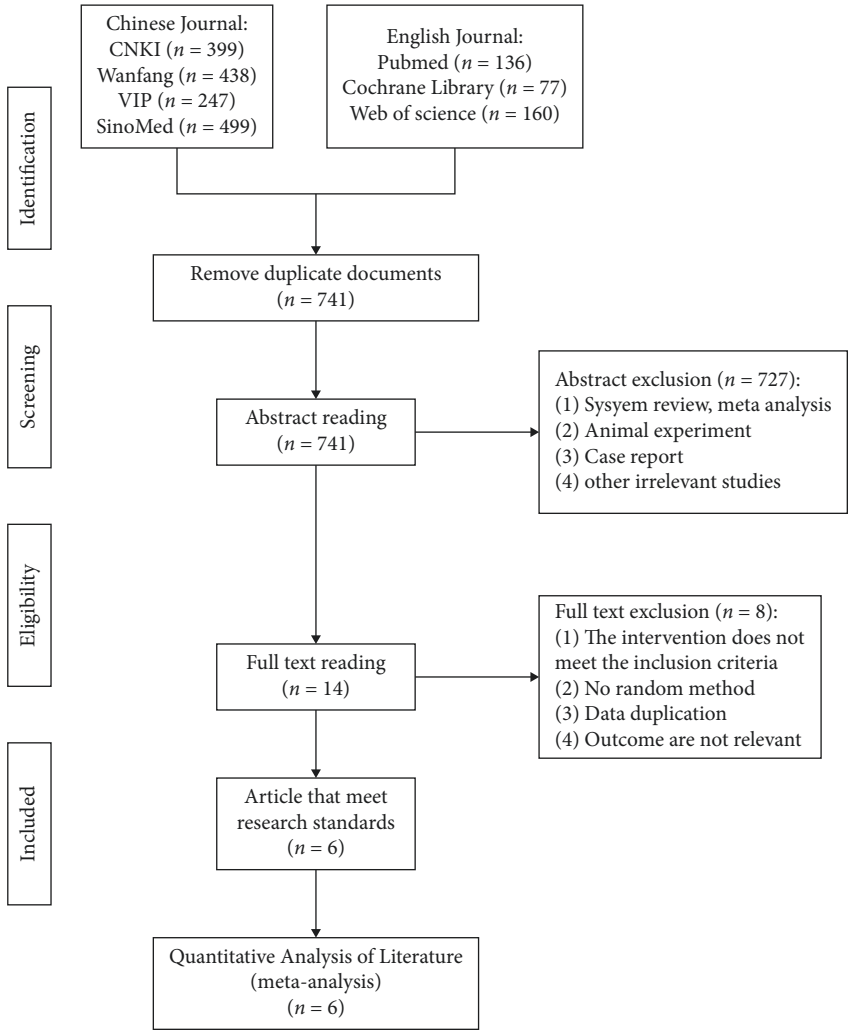


Figure 1: Flow diagram depicting the selection process of eligible studies. (CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journals Full-Text Database; SinoMed, the Chinese Biomedical Literature Database; *n* number of publications).

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

Table 1: Characteristics of included studies.

Study	Publish year	Sample		Intervention		Age (years)		Sex (M/F)		Disease course (days)		Outcome measure
		C	E	C	E	C	E	C	E	C	C	
Song [21]	2009	30	30	RT: Valaciclovir, 300 mg, orally three times daily for ten days; vitamin B1, 10 mg, orally three times daily for ten days	EA: EA on the Jiaji (EX-B2) + Zhigou (TE6) + Houxi (SI 3); sparse and dense waves (2/100 Hz), treatment duration was 30 minutes, once a day for ten consecutive days.	43.47 ± 13.57	42.23 ± 14.98	15/15	16/14	4.77 ± 1.76	5.10 ± 1.45	VAS, the time to cessation of pustules, scabs, rash healing, the incidence of postherpetic neuralgia
Li et al. [22]	2011	31	27	RT: Valaciclovir, 300 mg, orally twice daily for ten days; vitamin B1, 10 mg, orally three times daily for ten days	EA: EA on the ashi points + Jiaji (EX-B2); Zhigou (TE 6) + Houxi (SI 3); sparse and dense waves (2/100 Hz), treatment duration was 30 minutes, once a day for ten consecutive days.	49.61 ± 16.34	48.39 ± 17.06	24/7	16/11	4.87 ± 2.25	5.25 ± 2.01	VAS, the time to cessation of pustules, scabs, rash healing, and the incidence of postherpetic neuralgia
Lin [23]	2015	27	27	RT: Indomethacin, 25 mg, three times daily for seven days; valaciclovir, 300 mg, orally twice daily for seven days; vitamin B1, 10 mg, orally three times daily for seven days	RT + EA: EA on the Hegu (LI4) + Waiguan (TE 5); Yanglingquan (GB34) + Zulinqi (GB41) + Taichong (LR3), continuous-wave (20 minutes for 80 Hz, 10 minutes for 20 Hz), treatment duration was 30 minutes, once a day 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	VAS
Lu [24]	2017	12	13	RT: Diclofenac, 75 mg, orally once daily for ten days; mecobalamin, 0.5 mg, orally three times daily for ten days; valaciclovir, 250 mg, orally three times for ten days; external 3% boric acid solution	RT + EA: EA on the Jiaji (EX-B2), continuous wave (60 Hz), treatment duration was 30 minutes, once a day for ten consecutive days.	47.14 ± 10.34	47.28 ± 10.41	5/7	6/7	Not mentioned	Not mentioned	VAS, the time to cessation of pustules, scabs, and rash healing
Wei [25]	2019	45	45	RT: Valaciclovir, 0.3 g, orally twice daily for 14 days; adenosylcobalamin, 0.5 mg, orally three times for 14 days; pregabalin, 150 mg, orally twice daily for 14 days	RT + EA: (EA on the Jiaji (EX-B2) + local points of rash, continuous-wave (2 Hz), treatment duration was 30 minutes, once a day for 14 consecutive days.	56.53 ± 9.15	57.89 ± 8.22	22/23	20/25	Less than one week	Less than one week	VAS
Cheng [26]	2018	29	25	RT: Valaciclovir, 0.3 g, orally twice daily for ten days; methylcobalamin, 0.5 mg, orally three times for ten days; If the pain were severe, oxycodone (10 mg) would be used.	RT + EA: EA on the Jiaji (EX-B2) + local ashi points, continuous-wave (2 Hz), treatment duration was 30 minutes, once a day for ten consecutive days	61.1 ± 2.13	51.40 ± 3.12	17/12	12/13	4.72 ± 0.38	4 ± 0.36	VAS, the incidence of postherpetic neuralgia

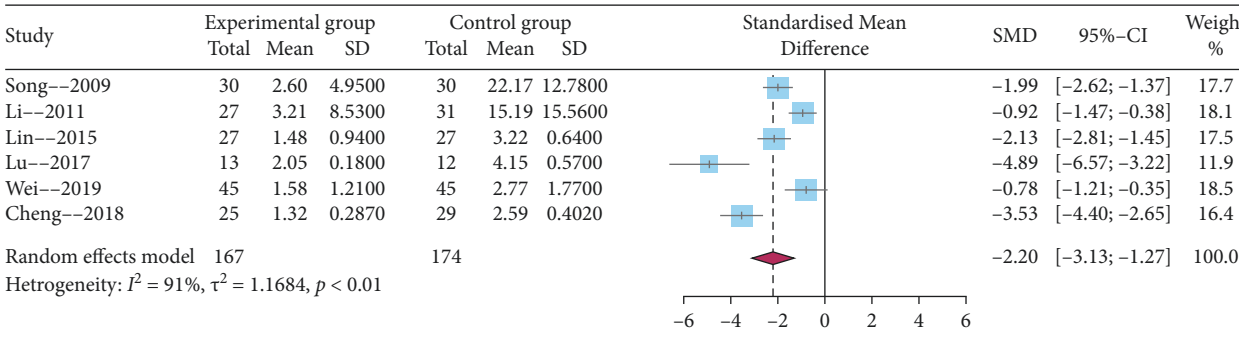
Abbreviations: C: control group; E: experimental group; VAS: visual analog scale.

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

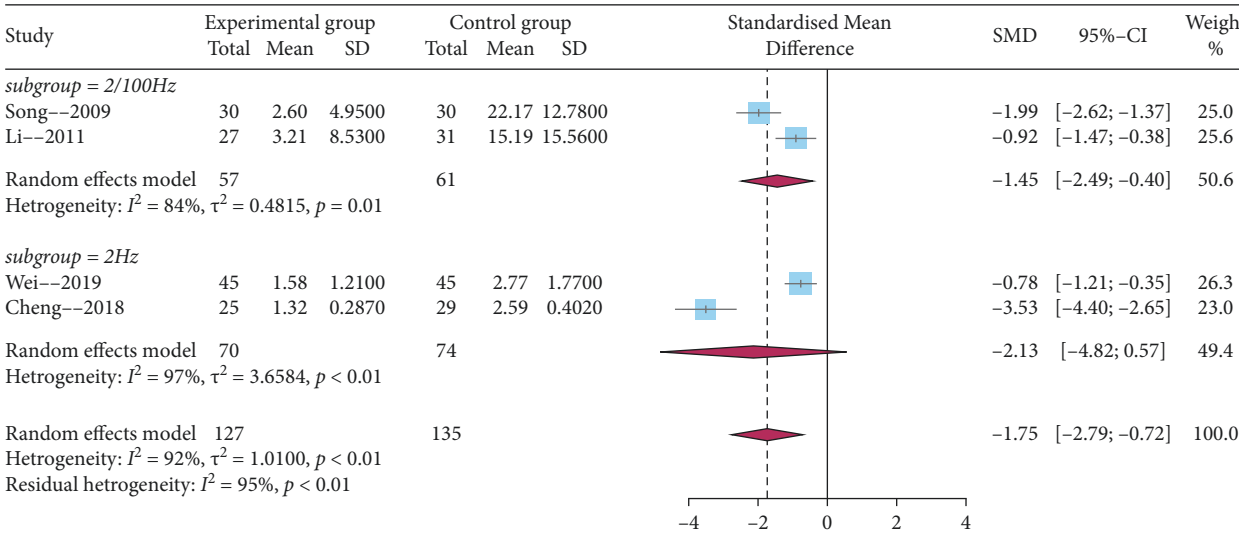
and was rated as unclear risk; one trial [25] did not mention randomization and was assessed as high risk. Concerning allocation, one study [22] provided the allocation concealment method in detail and was considered to be at a low risk of bias; five trials [21, 23–26] were rated as unclear risk of bias 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



(a)



(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

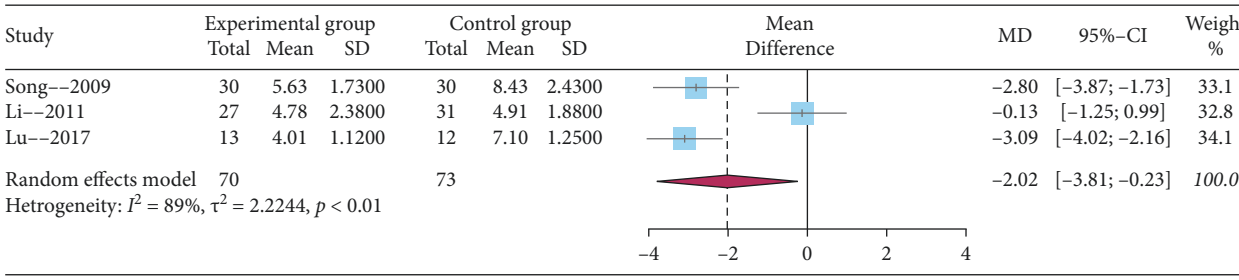


Figure 4: Funnel plot of the cessation of pustules time.

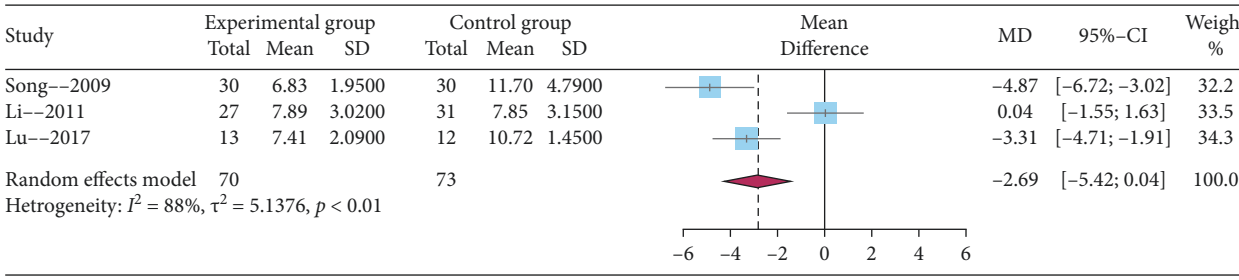


Figure 5: Funnel plot of the time to scab.

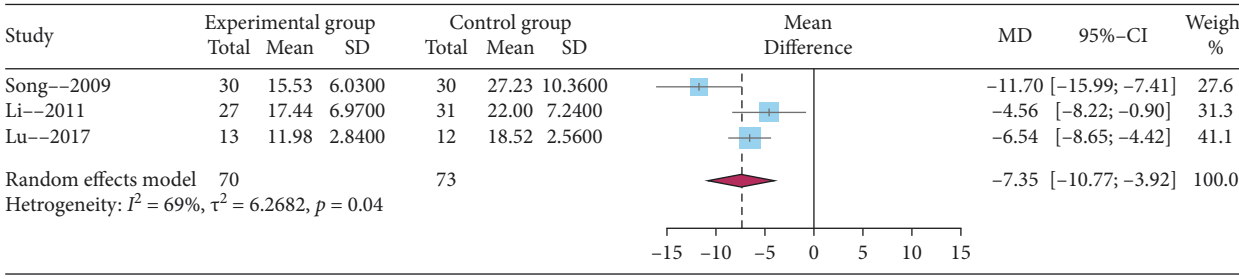


Figure 6: Funnel plot of the rash healing time.

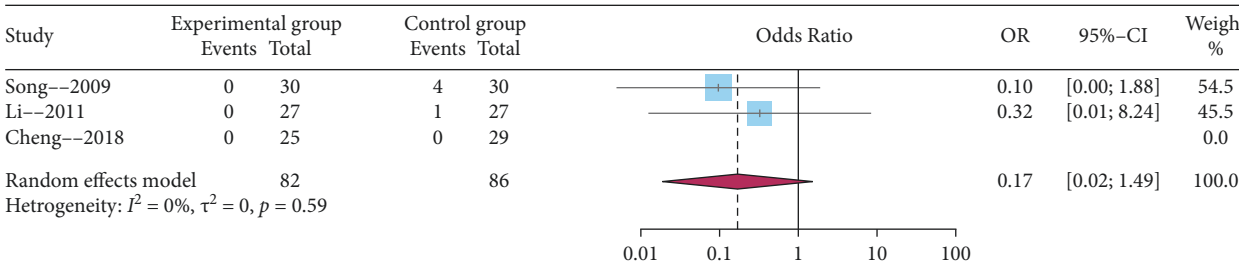


Figure 7: Funnel plot of the safety outcome.

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 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 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

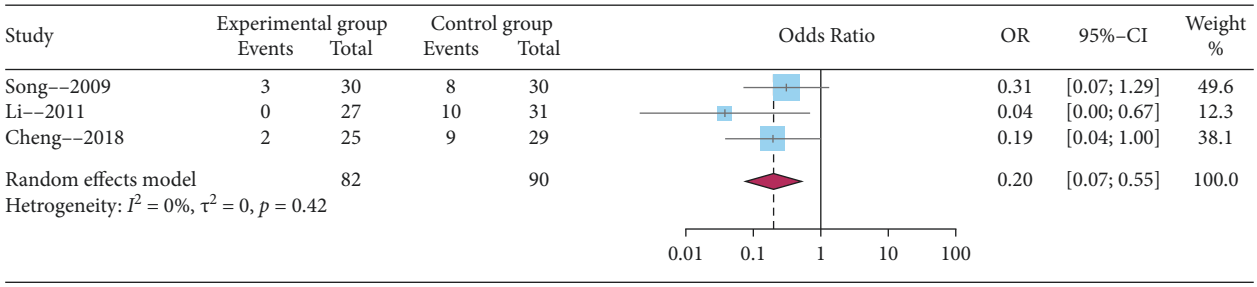


Figure 8: Funnel plot of the incidence of postherpetic neuralgia.

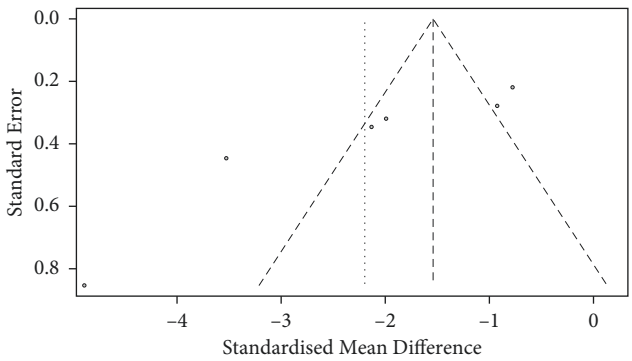


Figure 9: Meta-analysis results of publication bias.

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 meta-analysis 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 well-known 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.

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Supplementary Materials

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

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