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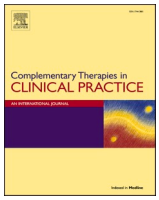

Acupuncture for the treatment of painful diabetic peripheral neuropathy: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: A growing number of studies have investigated the efficacy of acupuncture in the treatment of painful diabetic peripheral neuropathy (PDPN), but the findings of these studies have generated conflicting results. This study therefore aimed to assess the efficacy of acupuncture for treating PDPN so as to offer more conclusive results.

Methods: Seven databases were systematically searched for studies published up until December 1, 2023. All randomized controlled trials (RCTs) of acupuncture for PDPN with visual analog scale (VAS) for pain score were included. Study selection, data extraction, and evaluation were conducted independently by researchers. The Risk of Bias 2 (RoB2) tool was employed to assess the risk of bias. From this sample, the mean difference (MD), 95 % confidence intervals (CI), publication bias, and heterogeneity were then computed.

Results: The manual acupuncture group exhibited a significant decrease in the VAS for pain score compared with the routine care group ($p < 0.0001$; MD = −1.45 [95 % CI, −1.97 to −0.93], $I^2 = 84$ %). The real acupuncture group demonstrated a greater reduction in VAS scores than the sham acupuncture group ($p = 0.004$; MD = −0.97 [95 % CI, −1.63 to −0.31], $I^2 = 65$ %). Additionally, the acupuncture group showed improvements in sensory nerve conduction velocity (SNCV, $p < 0.0001$; MD = 2.29 [95 % CI, 1.79 to 2.78], $I^2 = 14$ %) as well as motor nerve conduction velocity (MNCV, $p < 0.0001$; MD = 2.87 [95 % CI, 2.46 to 3.27], $I^2 = 0$). Different durations of acupuncture treatment, including 6–10 weeks and 3–4 weeks, demonstrated a significant reduction in VAS scores compared with the routine care group.

Conclusion: This meta-analysis provides preliminary evidence for the claim that acupuncture has the potential to alleviate PDPN symptoms and improve SNCV and MNCV. However, high-quality RCTs are needed to offer further evidence and thus better substantiate such a contention.

1. Introduction

Diabetic peripheral neuropathy is a prevalent complication of diabetes mellitus and is characterized by a high incidence rate, significant disability among those with the disease, and a wide range of clinical symptoms. More than 50 % of patients diagnosed with diabetes mellitus were found to have diabetic peripheral neuropathy, which is recognized as a significant contributing factor to amputation in this patient population [1]. Painful diabetic peripheral neuropathy (PDPN) is a common form of diabetic peripheral neuropathy that affects approximately 15–25 % of individuals diagnosed with diabetes mellitus [2]. Patients with PDPN consistently exhibit both spontaneous and evoked pain [3]. Spontaneous pain is characterized by burning, shooting, or electric shock-like feelings, as well as lancinating, knife-like, crawling, or aching sensations [3]. Evoked pain, on the other hand, encompasses allodynia and paresthesia [3]. Comorbidities routinely associated with PDPN include sleep disturbance/insomnia, depressive symptoms, and anxiety [4,5]. The felt effects of these symptoms, however, extend well beyond the individual, as research has indicated that PDPN patients use a significant amount of healthcare resources related to diagnostic procedures, prescriptions, and interventional treatments [6]. Yet, despite the extent of healthcare services provided to PDPN patients, current research in this area lacks sufficient evidence to substantiate the effectiveness of intensive glycemic control and lifestyle interventions as a

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treatment for PDPN [7,8]. The American Academy of Neurology recommends that clinicians should offer gabapentin, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, tricyclic antidepressants, and SNRI/opioid dual-mechanism agents for treating PDPN [9]. However, evidence regarding the effect of these drugs on pain and quality of life is limited [9,10]. One study demonstrated that less than one in seven patients diagnosed with PDPN experienced significant pain relief [11]. Furthermore, other studies have determined that these medications are often associated with troublesome side effects, such as somnolence and dizziness [8,12,13].

Another possible therapeutic treatment for PDPN, outside of those listed above, is acupuncture. Acupuncture has been used as a therapeutic modality for the management of various painful conditions in China for centuries. With traditional acupuncture, the acupuncturist bases their selection of acupoints and treatment plan according to the patient's condition. Yet, even traditional acupuncture has been augmented through modern advancements, as practitioners have incorporated supplemental techniques into their practice, including electroacupuncture and laser acupuncture. In part due to its longstanding history, acupuncture has become the subject of extensive analysis. Several studies have demonstrated the potential benefits of acupuncture in various regards. As it concerns neuropathy and neuralgia, specifically, many studies have shown that acupuncture can enhance nerve conduction velocity [14], alleviate neuropathic pain [15,16], improve sleep quality [17], and potentially reduce the required dosage of pain medication [18]. However, the aforementioned studies examined the use of acupuncture for neuralgia caused by several different diseases, only one of which was diabetes. Whether acupuncture has a definitive therapeutic effect on PDPN, though, remains controversial. To date, no systematic review has been conducted to rigorously evaluate the effect of acupuncture on PDPN. Further complicating matters is the fact that, there are discrepancies in the most recent clinical guidelines provided for treating PDPN with acupuncture [19]. Therefore, a primary objective of this systematic review and meta-analysis was to examine the impact of acupuncture on PDPN and assess the effects on sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) through an analysis of randomized controlled trials (RCTs), with an ancillary benefit being more informed guidance on the clinical applications of acupuncture for PDPN.

2. Methods

The protocol for this article was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42022359973. Registration details may be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=359973.

2.1. Search strategy

This systematic review was conducted according to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [20]. In accordance with this statement, relevant publications assessing the impact of acupuncture on PDPN were systematically searched in multiple databases, including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), the Chinese Biomedical Literature Database, the VIP Information Database, the Chinese National Knowledge Infrastructure, and Wanfang Database. The search encompassed articles published from the inception of these databases until December 1, 2023. We employed the following three grouped terms in search strategy, which were modified to suit each database: 1) acupuncture, acupuncture therapy, auricular acupuncture, meridians, needling, AND/OR needling; 2) painful diabetic neuropathy, diabetic neuropathies, diabetic neuropath*, "painful diabet*, AND/OR pdn; and 3) clinical trial, AND/OR randomized controlled trial (supplementary materials, search strategy). This search was complemented by an additional search of gray literature, which was conducted using Bing, OPENGREY.EU and ProQuest Dissertations & Theses. No language restrictions were placed on the search results. These searches were performed by two of this article's co-authors (YZF and CLW), who independently searched the electronic databases previously referenced.

2.2. Inclusion criteria

2.2.1. Participants

The participants featured in the studies included in this review were adult patients diagnosed with PDPN. PDPN, in this context, is defined as a pain symptom resulting from damage to peripheral somatic sensatory mechanisms as caused by diabetes.

2.2.2. Interventions

The treatment groups in the selected studies received manual acupuncture, electroacupuncture, or laser acupuncture.

2.2.3. Controls

The control groups were treated with sham acupuncture or routine care for PDPN.

2.2.4. Outcomes

The primary outcome was the visual analog scale (VAS) for pain score. Additional outcomes included SNCV and MNCV.

2.2.5. Study design

The studies included in our analyses were limited to RCTs.

2.3. Exclusion criteria

Patients with neuropathic pain resulting from diseases other than diabetes, and those undergoing acupuncture-related therapies such as moxibustion, acupoint injection, warm needling, and auricular acupuncture were not considered eligible for inclusion in this review.

2.4. Study selection and data extraction

Two authors (YZF and CLW) independently reviewed all titles and abstracts according to the design outlined above. If a consensus between the two authors could not be reached, a third author (GTL) adjudicated upon the inclusion of the articles in question. Two other authors (HG and QW) independently extracted the data from each study included in the dataset. The trial reports selected for inclusion featured the following information: sample size, demographic characteristics (age and sex), average duration of diabetes mellitus or PDPN, description of interventions used, treatment duration, outcomes, and study location (Table 1).

2.5. Assessment of risk of bias

According to the Cochrane Collaboration's tool [21], the risk of bias for all the studies included in this review was independently evaluated by two authors (YZF and CLW) using the Risk of Bias 2 (RoB2) tool [22]. The biases encompassed the following six domains: 1) randomization process, 2) deviations from intended interventions, 3) missing outcome data, 4) outcome measurements, 5) selection of reported result, and 6) overall bias. Each domain was categorized as low, high, or some concerns risk of bias.

2.6. Statistical analysis

We performed our analysis of the data using RevMan 5.4.1 software for Windows. The data were combined using a random-effects model when I^2 was greater than 50 %. Otherwise, a fixed-effects model was used. Given that the VAS score, SNCV, and MNCV function as continuous

Table 1
The detailed characteristics of the included studies.

References	Sample size	Age (years)	Gender (male/female)	Mean duration of diabetes or PDPN (years)	Intervention		Treatment duration	Outcome measures	Location
	acupuncture/control	acupuncture/control	acupuncture/control	acupuncture/control	acupuncture	control			
Adam 2014	24/21	68 ± 11.1/63 ± 10.8	(16/8)/(15/6)	Diabetes:12.2 ± 7.4/11.0 ± 9.2 PDPN: Not reported	MA	SA	10 weeks	VAS, AEs	U.K.
Cao 2015	31/29	58.45 ± 9.15/60.83 ± 9.54	(20/11)/(12/17)	Diabetes:8.00 ± 3.95/9.10 ± 1.56 PDPN: Not reported	MA + RC	RC	8 weeks	VAS, MNCV, SNCV	China
Deng 2021	30/30	59 ± 9/57 ± 9	(18/12)/(15/15)	Diabetes:10.4 ± 3.9/9.3 ± 3.6 PDPN:3.8 ± 2.6/3.0 ± 2.3	MA + RC	RC	4 weeks	VAS, MNCV, SNCV	China
Hou 2018	40/40	54.92 ± 10.65/59.76 ± 9.43	(19/21)/(20/20)	Not reported	MA + RC	RC	4 weeks	VAS, MNCV, SNCV	China
Hu 2017	47/47	58.92 ± 6.31/59.73 ± 6.90	(26/21)/(25/22)	Diabetes:10.25 ± 1.49/11.09 ± 1.83 PDPN:4.93 ± 0.84/5.36 ± 1.07	MA + RC	RC	4 weeks	VAS, MNCV, SNCV, AEs	China
Jonas 2017	30/30	48.21 ± 8.36/47.97 ± 9.47	(15/15)/(14/16)	Diabetes:4.72 ± 1.19/5.04 ± 4.51 PDPN: Not reported	MA + RC	RC	8weeks	VAS	China
Li 2018	100/100	55.20 ± 7.83/54.44 ± 8.8	(48/52)/(43/57)	Diabetes:4.9/5.6 PDPN:2.3/2.2	MA + RC	RC	3 weeks	VAS, MNCV, SNCV	China
Liu 2016	28/28	46.20 ± 15.25/43.25 ± 13.35	(8/20)/(10/18)	Diabetes:13.93 ± 3.11/13.50 ± 3.86 PDPN: Not reported	EA + RC	RC	4 weeks	VAS	China
He 2017	40/40	51.7 ± 9.2/49.2 ± 6.7	(18/22)/(16/24)	Diabetes:10.5 ± 7.2/11.4 ± 5.0 PDPN: Not reported	EA + RC	RC	6 weeks	VAS, MNCV, SNCV	China
Shahzad 2014	62/50	51.54 ± 10.46/51.70 ± 11.43	not reported	Not reported	LA + RC	SA + RC	8 weeks	VAS, AEs	Pakistan
Shahzad 2014*	62/52	51.54 ± 10.46/49.38 ± 10.56	not reported	Not reported	LA + RC	Amitriptyline + RC	8 weeks	VAS, AEs	Pakistan
Joanna 2023	31/31	66.7 ± 7.6/69.5 ± 7.2	(25/6)/(24/7)	Not reported	MA + RC	RC	8 weeks	VAS, AEs	Germany
Liu 2020	30/30	61.36 ± 3.08/61.89 ± 3.57	(13/17)/(15/15)	Diabetes: 6.98 ± 1.85/7.68 ± 1.24	MA + RC	RC	4 weeks	VAS	China
Peng 2016	43/43	56.39 ± 4.63/57.52 ± 5.26	(27/16)/(25/18)	Diabetes: Not reported PDPN:1.15 ± 0.41/1.23 ± 0.32	MA + RC	RC	4 weeks	VAS	China
Shu 2021	9/12	64.0 ± 8.0/65.0 ± 7.0	(15/15)/(19/11)	Diabetes: 12.5/19.5 PDPN:2.0/1.0	MA + RC	RC	4 weeks	VAS	China
Zardosht 2023	30/30	49.86 ± 6.43/50.20 ± 6.91	(11/19)/(12/18)	Not reported	MA + RC	SA + RC	7 weeks	VAS, AEs	Iran

PDPN: painful diabetic peripheral neuropathy; MA: manual acupuncture; EA: electroacupuncture; LA: laser acupuncture; SA: sham acupuncture; RC: routine care; VAS: visual analog scale; AEs: adverse effects; SNCV: sensory nerve conduction velocity; MNCV: motor nerve conduction velocity.

variables, the mean difference (MD) was employed as a summary statistic when outcomes were reported on the same scale. However, if the same outcomes were measured on different scales, the standardized mean difference (SMD) was used. All data were summarized using 95 % confidence intervals (CI). There was a significant difference if the value of p was <0.05 between the two groups. We employed I^2 and χ^2 tests to evaluate the presence of heterogeneity. Heterogeneity was classified based on the I^2 index values. Heterogeneity was considered low when the I^2 index values ranged from 25 % to 50 %. Moderate heterogeneity was defined as an I^2 value between 51 % and 75 %. High heterogeneity was indicated by I^2 index values of >75 %. Publication bias was assessed using Egger's regression intercept test and Begg's test.

2.7. GRADE evaluation

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADEpro) Guideline Development Tool (GDT) to assess the quality of primary and secondary outcomes with the following domains: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations.

3. Results

3.1. Study selection

An initial search conducted by CLW and YZF across seven databases, resulting in the identification of 762 potentially relevant articles. We also searched websites for gray literature and eliminated 44 articles because they were conference proceedings or studies that did not qualify as RCTs. After eliminating duplicate studies, 575 studies remained. This subset of applicable studies was further winnowed after reviewing article titles and abstracts, resulting in the exclusion of 425 articles. Case reports, case series, reviews, animal studies, and studies deemed irrelevant to PDPN were also excluded. In the subsequent analysis, we excluded studies that did not meet the criteria of an RCT or that included patients that were treated with acupuncture-related therapy but did not have PDPN, leading to the exclusion of 86 articles. The remaining 64 were selected for further investigation. After thoroughly examining each article, 15 trials were ultimately incorporated into the dataset [23–37]. The study selection process is illustrated in Fig. 1.

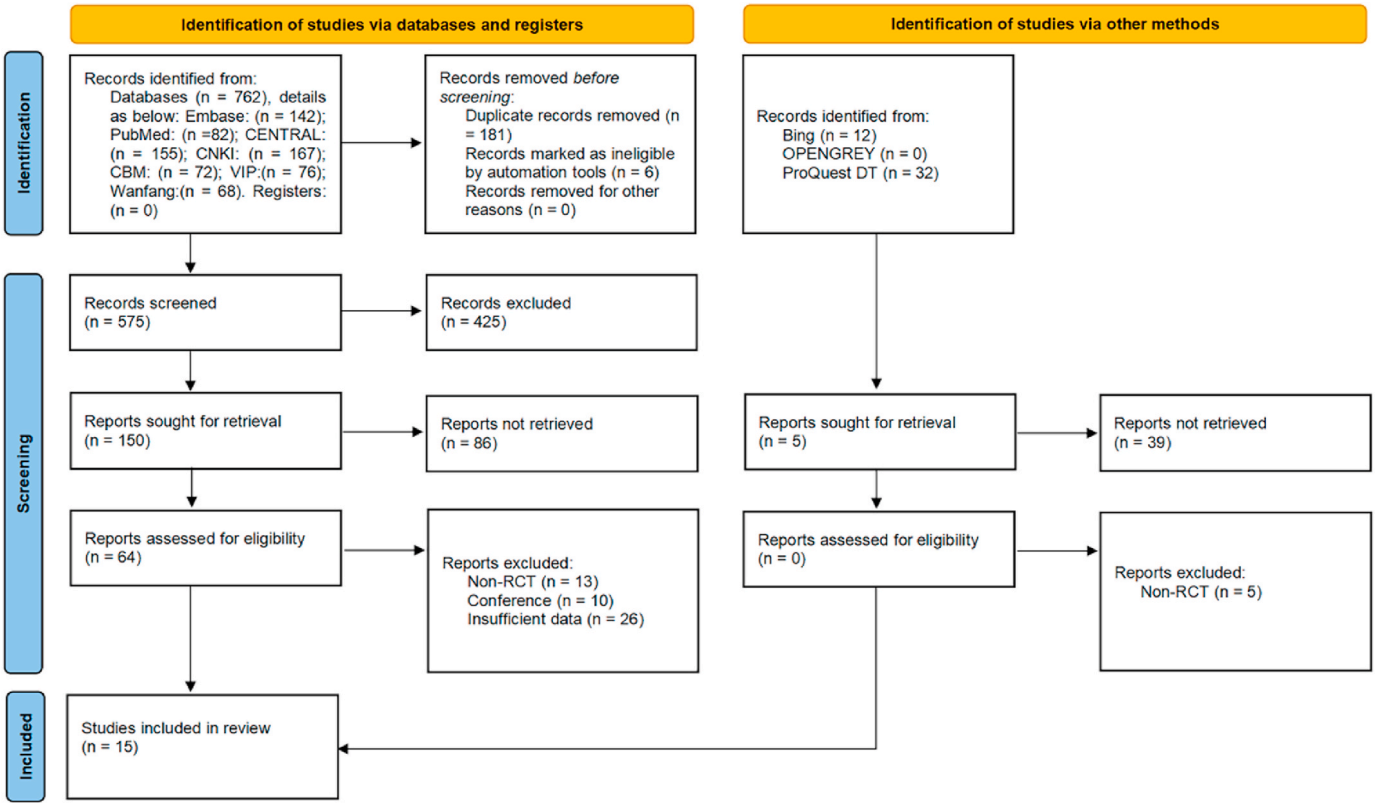

Fig. 1. Flow chart of the study selection process. RCT: randomized controlled trial; ProQuest DT: ProQuest Dissertations & Theses.

3.2. Study characteristics

The fundamental attributes of the 15 studies are summarized in Table 1. Of these 15, 11 single-center trials were conducted in China and subsequently published in Chinese journals where the primary language medium is Mandarin. The remaining four studies were conducted in Pakistan, the United Kingdom, Germany, and Iran and found outlets in journals publishing in English. A total of 1186 participants were included in the analysis, with sample sizes ranging from 21 to 200. Among all of the studies examined, only one study included the use of two control groups [31]. Moreover, most clinical trials did not distinguish type 1 diabetes patients from type 2 patients, and instead chose to group them together. The average patient age varied between 43.25 and 68 years old, and the average duration of the disease since initial onset ranged from 4.72 to 13.9 years. However, data on the duration of PDPN, specifically, were limited. The course of treatment represented in these studies ranged from 3 to 10 weeks. Manual acupuncture was employed in 12 trials [23–25,27–30,32–36], electroacupuncture in two trials [26,37], and laser acupuncture in one trial [31]. Although various studies employed other interventional methods in both the experimental groups and control groups, such as the oral administration of Chinese herbal medicine, eight-section brocade exercises, foot baths, or infrared radiation, the primary objectives of these treatments were rooted in the principles of traditional Chinese medicine and so sought to enhance blood circulation and eliminate blood stasis. Regardless of the intervention detailed, though, all of these studies reported a VAS score, and six reported on patients' SNCV and MNCV.

3.3. Risk of bias in the included studies

According to the predefined criteria established in the RoB2 tool, two trials exhibited a low risk of bias [23,36] in that they provided a clear description of the randomization method used, whereas some concerns remained for the other 13 trials. Among those trials included in the dataset, only four trials were conducted in a double-blind manner [23,25,35,36], and an additional 11 trials described their randomization process in more general terms, without detailing the specifics of their methodological approach. Owing to the use of sham acupuncture as a control, two trials demonstrated no deviations from intended interventions [23,36]. Another 13 trials did not employ double-blind procedures and therefore were categorized as possessing an uncertain risk of bias. All trials offered outcome data and performed appropriate statistical analyses. Three trials made their protocols and registrations publicly available [23,35,36], whereas the remaining 12 trials failed to offer such detailed information. Fig. 2 depicts these various risks of bias in graph form, whereas Fig. 3 offers a summary of the risk of bias.

3.4. Efficacy assessment

The results of 10 trials demonstrated a significant decrease in the VAS score in the manual acupuncture group compared to the routine care group ($p < 0.0001$; MD = −1.45 [95 % CI, −1.97 to −0.93]; Fig. 4) [24,25,27–30,32–35]. Heterogeneity analysis indicated high heterogeneity ($\chi^2 = 55.30$, df = 9 [$p < 0.0001$]; $I^2 = 84$ %). Sensitivity analyses demonstrated that the stability of the results remained unaffected even when individual studies were excluded because of their large MD (supplementary materials, sensitivity analyses). In addition, subgroup analyses were conducted to investigate potential sources of heterogeneity and evaluate the impact of course of treatment on the observed outcomes. Three to four weeks of acupuncture treatment showed a significant decrease in the VAS score reported ($p < 0.0001$; MD = −1.14 [95 % CI, −1.62 to −0.67]; Fig. 5) [25,27,28,30,32–34], as did treatment courses ranging from 6 to 10 weeks ($p < 0.0001$; MD = −2.12 [95 % CI, −3.70 to −0.53]; Fig. 6) [24,29,35]. The real acupuncture group demonstrated a greater reduction in VAS scores compared to the sham acupuncture group ($p = 0.004$; MD = −0.97 [95 % CI, −1.63 to −0.31]; Fig. 7) [23,31,36].

The findings from six trials [24–28,30] indicated that acupuncture

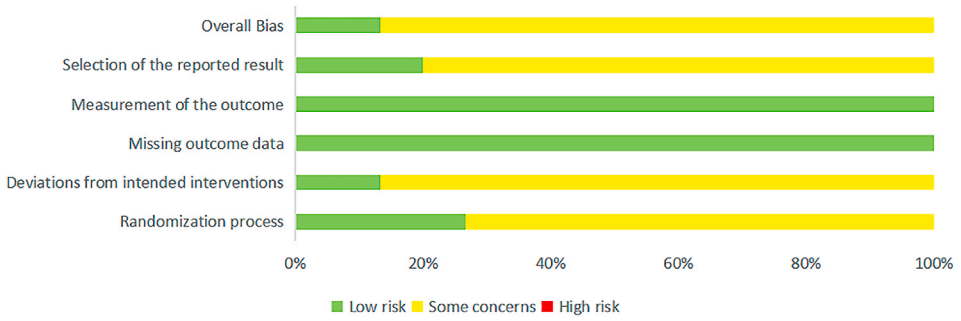

Fig. 2. Risk of bias graph.

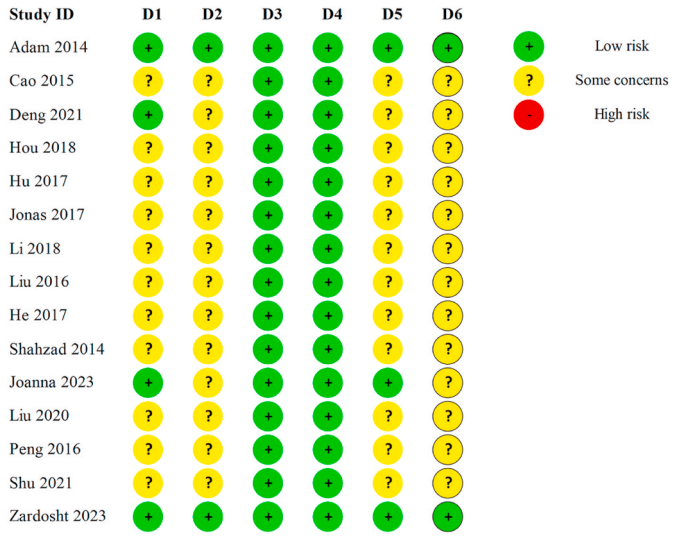

Fig. 3. Risk of bias summary. ID: identification; D1: randomization process; D2: deviations from intended interventions; D3: missing outcome data; D4: outcome measurements; D5: selection of reported result; D6: overall bias.

was significantly more effective in improving SNCV than routine care ($p < 0.0001$; MD = 2.15 [95 % CI, 1.80 to 2.50]; Fig. 8). The level of heterogeneity observed was mild and within acceptable limits (heterogeneity: $\chi^2 = 5.8$, df = 5 [$p = 0.33$]; $I^2 = 14$ %).

Regarding MNCV, the findings from six trials [24–28,30] indicated that acupuncture demonstrated greater effectiveness than routine care ($p < 0.0001$; MD = 2.87 [95 % CI, 2.46 to 3.27]; Fig. 9). Furthermore, there was no observed heterogeneity (heterogeneity: $\chi^2 = 2.65$, df = 5 [$p = 0.75$]; $I^2 = 0$).

3.5. Publication bias

Egger's regression intercept test ($p = 0.002$) and Begg's test ($p = 0.005$) were conducted to investigate publication bias using R software, version 3.4.2 (R Foundation). These results suggest that publication bias may have influenced the observed results. This being the case, the Duval and Tweedie's trim and fill procedure nonetheless showed that the manual acupuncture group remained statistically significant after adjusting for potential publication bias ($p = 0.004$; SMD = −0.627 [95 % CI, −0.1950 to −1.0595]; Fig. 10). In conclusion, although the observed results may have been influenced by publication bias, there was no evidence of a small study effect, and the end result was still stable.

3.6. Adverse effects

Five studies [23,28,31,35,36] reported minor and transient adverse effects, including fatigue and swelling at the acupoints, with the extent of reporting remaining variable across these studies. However, of those that did report such adverse effects, none required medical intervention. The remaining studies did not mention any adverse effects. As a result of insufficient data of adverse effects, we decided to conduct a descriptive, rather than a quantitative, analysis.

3.7. Certainty of evidence

Due to concerns regarding the risk of bias and high heterogeneity, the quality of evidence for manual acupuncture treatments for PDPN was deemed very low, as was the quality of evidence for the subgroup of different durations of acupuncture treatment. As for the real acupuncture versus sham acupuncture, the quality of evidence was moderate, primarily on account of the risk of bias. The quality of evidence on nerve conduction velocity, however, was high. A summary of these findings is provided in Fig. 11.

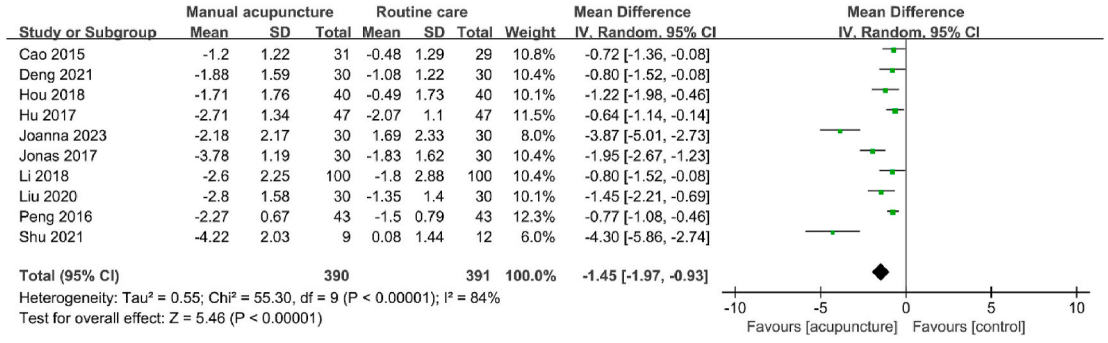

Fig. 4. Forest plot of acupuncture for pain relief as compared with routine care. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

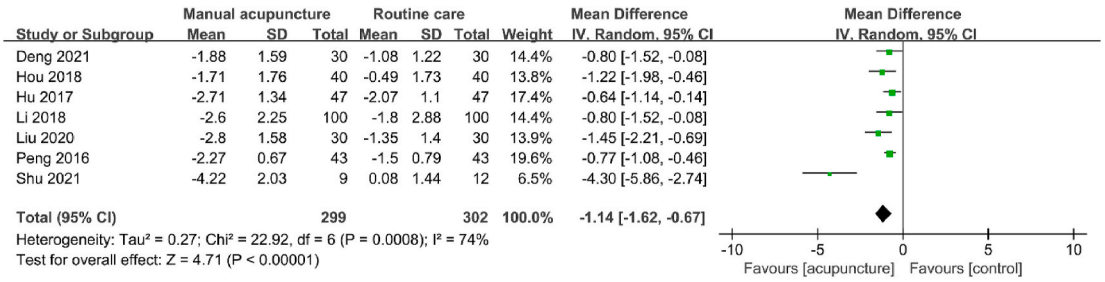

Fig. 5. Forest plot of 3–4 weeks of manual acupuncture for pain as compared with routine care. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

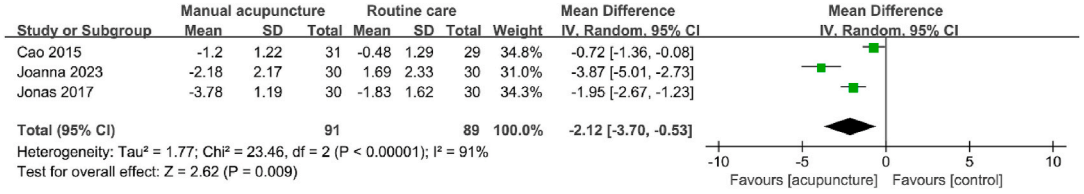

Fig. 6. Forest plot of 6–10 weeks of manual acupuncture for pain as compared with routine care. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

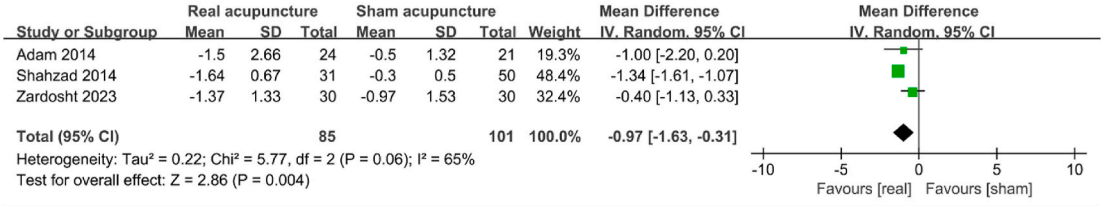

Fig. 7. Forest plot of real acupuncture for pain as compared with sham acupuncture. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

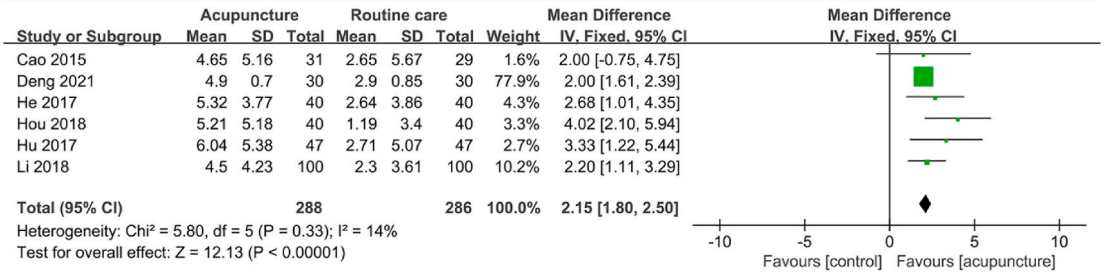

Fig. 8. Forest plot of acupuncture for SNCV as compared with routine care. SNCV: sensory nerve conduction velocity; SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

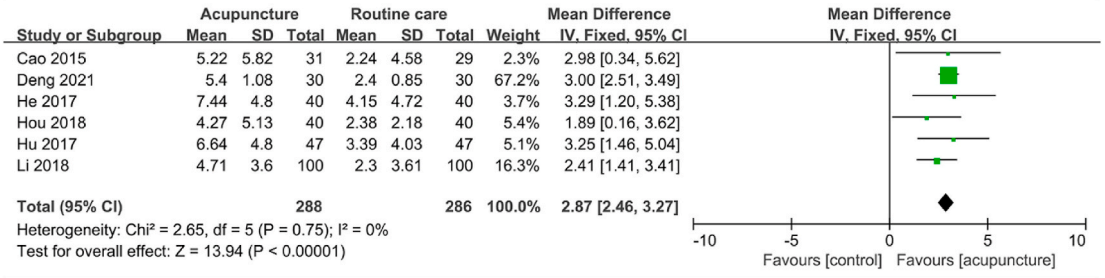

Fig. 9. Forest plot of acupuncture for MNCV as compared with routine care. MNCV: motor nerve conduction velocity; SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degree of freedom.

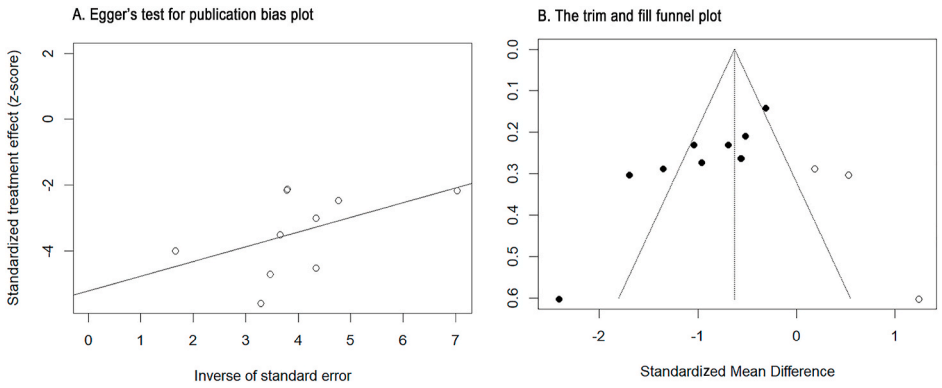

Fig. 10. (A): Egger's test for publication bias plot and (B): The trim and fill funnel plot.

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With Acupuncture		Risk with control	Risk difference with Acupuncture
manual acupuncture versus routine care (follow-up: range 3 weeks to 10 weeks; assessed with: VAS score)											
781 (10 RCTs)	serious[a]	serious[b]	not serious	not serious	publication bias strongly suspected[c]	⨁◯◯◯ Very low[d]	391	390	-	391	MD **1.45 lower** (1.97 lower to 0.93 lower)
real acupuncture versus sham acupuncture groups (follow-up: range 3 weeks to 10 weeks; assessed with: VAS score)											
186 (3 RCTs)	not serious	serious[e]	not serious	not serious	none	⨁⨁⨁◯ Moderate[d]	101	85	-	101	MD **0.97 lower** (1.63 lower to 0.31 lower)
SNCV											
574 (6 RCTs)	serious[a]	not serious	not serious	not serious	strong association	⨁⨁⨁⨁ High[f]	286	288	-	286	MD **2.15 higher** (1.8 higher to 2.5 higher)
MNCV											
574 (6 RCTs)	serious[a]	not serious	not serious	not serious	strong association	⨁⨁⨁⨁ High[f]	286	288	-	286	MD **2.87 higher** (2.46 higher to 3.27 higher)
6-10 weeks of treatment duration (follow-up: range 6 weeks to 10 weeks; assessed with: VAS score)											
180 (3 RCTs)	serious[a]	serious[g]	not serious	not serious	none	⨁⨁◯◯ Low[h]	89	91	-	89	MD **2.12 lower** (3.7 lower to 0.53 lower)
3-4 weeks of treatment duration (follow-up: range 6 weeks to 10 weeks; assessed with: VAS score)											
601 (7 RCTs)	serious[a]	serious[i]	not serious	not serious	publication bias strongly suspected[c]	⨁◯◯◯ Very low[d]	302	299	-	302	MD **1.14 lower** (1.62 lower to 0.67 lower)

CI: confidence interval; **MD:** mean difference

Explanations

a. Most information was accompanied by an unclear risk of bias
b. The heterogeneity analysis indicated high heterogeneity with I^2 = 84%
c. The Egger's test identified publication bias to be present
d. Further research is likely to have an important impact on the estimation of effects and may alter said estimates
e. The heterogeneity analysis indicated moderate heterogeneity with I^2 =65%
f. Further research is very unlikely to change our confidence in the estimation of effects
g. The heterogeneity analysis indicated high heterogeneity with I^2 = 91%
h. Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
i. The heterogeneity analysis indicated high heterogeneity with I^2 = 74%

Fig. 11. Summary of the findings table linked to GRADEpro. VAS: visual analog scale; RCT: randomized controlled trial; SNCV: sensory nerve conduction velocity; MNCV: motor nerve conduction velocity; CI: confidence interval; MD: mean difference.

4. Discussion

4.1. Summary of findings and quality of the evidence presented

We conducted a meta-analysis that provides evidence supporting the efficacy of manual acupuncture in alleviating pain associated with diabetic peripheral neuropathy, yet the certainty of evidence (CoE) was very low. This being the case, acupuncture may still be recommended for the purposes of pain relief, as its adverse effects were reported to be both minor and transient. The group receiving real acupuncture, however, demonstrated a greater reduction in reported VAS scores than the sham acupuncture group, with a moderate CoE. The favorable effects of manual acupuncture were seen with both a three to four weeks treatment duration (very low CoE) and a six to ten weeks treatment duration, though the CoE for this group remains low. Additionally, the majority of the trials included in our analyses did not describe detailed blinding procedures or make their protocols public, which led to further concerns regarding the risk of bias. Other concerns for the integrity of the data stem from, the moderate-to-high heterogeneity exhibited by the pooled data, which also degrades the CoE. When it came to improving SNCV and MNCV, acupuncture demonstrated a high degree of effectiveness with a high CoE, supporting the contention that acupuncture should be recommended to improve nerve conduction velocity.

4.2. Interpreting the findings in relation to other reviews or studies

An overview of 18 systematic reviews demonstrated that acupuncture may improve symptoms associated with diabetic peripheral neuropathy [38]. However, it was unable to perform further quantitative analyses. A recent meta-analysis reached a conclusion similar to ours [39]. It is important to point out, though, that in this particular review [39], moxibustion therapy and acupoint injections were not excluded. Moxibustion utilizes heat to stimulate acupoints by burning mugwort leaves, making this type of therapy different from more straightforward acupuncture. Acupoint injection is likewise a variation of acupuncture that involves locally injecting therapeutic drugs into an acupoint, as opposed to simply using needles to stimulate an acupoint. As a result, the therapeutic effect of acupoint injection does not come from acupuncture alone. Considering the high representation of acupuncture variations in the literature, we therefore ensured that only acupuncture that did not include auxiliary therapeutic agents or techniques was included in our meta-analysis to avoid clinical heterogeneity. One meta-analysis, however, stood out for its promising findings regarding the use of just acupuncture for pain relief for diabetic peripheral neuropathy [40]. That said, the authors offered few clinically relevant conclusions due to high heterogeneity of their data and the presence of publication bias [40].

We also incorporated two recent published high-quality RCTs into our meta-analysis to promote the timeliness of our research [35,36]. While our meta-analysis was designed to minimize clinical heterogeneity by establishing strict inclusion and exclusion criteria, we also performed subgroup analysis and sensitivity analysis to evaluate the reliability of the results. Additionally, acknowledging that our review also is susceptible to publication bias, we adjusted our analyses by performing trim and fill procedure, which showed that the results maintained stability.

In addition to examining studies focused on acupuncture for diabetic nerve pain, we also looked at those that investigated nerve conduction. Nerve conduction velocity was used to diagnose nerve fiber pathologies by one nerve conduction study [41], particularly resulting from diabetic neuropathy. Two studies have suggested that nerve conduction studies could be used as the basis for screening, evaluating, and monitoring with patients with diabetic peripheral neuropathies [42,43]. Therefore, we conducted further evaluations of nerve conduction velocity in our analyses. Our findings showed that when compared with the control group, acupuncture resulted in a significant increase in both SNCV and MNCV.

4.3. Potential mechanisms

In this meta-analysis, 30 acupoints, as presented in Table 2, were chosen for the purpose of pain relief. Primary acupoints were derived from the meridians located along bladder, stomach, spleen, and gallbladder. All four meridians traverse the lower limbs and feet frequently cited areas of pain for patients with PDPN. Additional acupoints were situated in the dorsal region (BL13, BL17, BL20, and BL23) and the upper extremities (PC6, PC7, HT7, LI4, LI11, and SJ5). These acupuncture points serve as a means of treating the meridians from a distance, a common practice that is in alignment with the holistic principles of traditional Chinese medicine. While these practices are rooted in a centuries-old form of traditional Chinese medicine, it is gaining traction as a viable, and empirically proven, treatment option within mainstream allopathic medicine. In fact, two recent studies found that acupuncture could mediate neuroimmune crosstalk between the peripheral and central nerves and regulate signal transduction to relieve pain [44,45].

4.4. Limitations

A primary limitation of this study lies in its use of the VAS score as a reliable indicator of pain relief. As a composite outcome, the VAS score is limited in its ability to evaluate the actual effect of acupuncture on PDPN. Highlighting the shortcomings of composite outcomes, one review identified several errors in data extraction for meta-analysis that possibly occurred when composite outcomes were reported in trials [46]. Granted, the possibility for error in composite outcomes was measured in meta-analyses of cardiovascular trials in the case of that review, so whether meta-analyses of pain scores are subject to the same analytical pitfalls remains unknown [46]. Due to complicated clinical features of PDPN, outcome indicators in our meta-analysis were limited. The Leeds assessment of neuropathic symptoms and signs pain scale, neuropathic pain symptom inventory and neuropathy total symptom

Table 2
The number of RCTs containing the acupoint.

Acupoints	RCT
ST36	11
SP6	10
GB34	6
KI3	6
SP10	4
LI4	4
SP9	4
LI11	3
LR3	3
GB39	2
ST40	2
BL17	2
BL20	2
BL23	2
HT7	1
PC7	1
BL60	1
BL13	1
GB31	1
ST41	1
PC6	1
SJ5	1
ST34	1
EX-LE-10	1
SJ3	1
SJ4	1
LI5	1
SI3	1
KI6	1
ST44	1

RCT: randomized controlled trial.

scale were not included. Although strict inclusion and exclusion criteria were established to minimize clinical heterogeneity, there was nonetheless high statistical heterogeneity in our meta-analysis, which may be attributed to the differences in the acupuncturists' respective professional background, and in their acupoint selection, as well as the small sample size of articles included in this review. It is also worth noting that the majority of studies included in this review met with some concerns of risk of bias when they were estimated by RoB2 tool. Taking the heterogeneity and issues with the RoB2 tool application together, then, the CoE qualifies as very low. Another limitation to our analyses is that only five studies [23,28,31,35,36] reported minor and transient adverse effects, but did so without providing greater detail, compelling us to conduct a descriptive analysis.

4.5. Implications for future studies

Elaborating further on the CoE, the scores observed for real acupuncture versus sham acupuncture were higher than those for manual acupuncture versus routine care. This may be attributed to the fact that, when evaluated against the efficacy of real acupuncture, sham acupuncture makes for a more appropriate blind protocol [47]. Future research should also take care to document and report any adverse effects observed in clinical trials. Therefore, we advise future studies to use sham acupuncture as a control and ensure that their reporting practices are in strict accordance with the Comprehensive Criteria for Reporting Trials (CONSORT) statement and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [48,49]. Another point to consider for future work in this area is that meta-analyses of individual participant data (IPD-MA) far surpasses aggregate data meta-analyses in terms of reliability [50]. IPD-MA can confirm the treatment plans prescribed for the study subjects, thereby better ensuring both the accuracy and integrity of the data [50]. As a result, IPD-MA may be a worthwhile research avenue to pursue to confirm the effects of acupuncture on PDPN.

5. Conclusion

This meta-analysis indicates that manual acupuncture is possibly more effective than routine care in relieving pain. However, the certainty of evidence supporting such a claim is low due to the mitigating effects of risk of bias and inconsistency in results. Despite the lack of certainty surrounding acupuncture's pain-relieving properties, though, it may still significantly improve nerve conduction velocity when compared to routine care.

CRediT authorship contribution statement

Chunliang Wang: Writing – review & editing, Methodology, Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **Yuzhu Fan:** Writing – original draft, Formal analysis, Data curation, Investigation. **Guiting Liang:** Funding acquisition, Supervision, Validation. **Qiang Wang:** Data curation, Formal analysis. **Hui Gao:** Data curation, Formal analysis. **Junhong Duan:** Visualization, Data curation, Project administration, Resources.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2024.101889.

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