Complementary Therapies in Medicine 78 (2023) 102992

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Effects of acupuncture therapy in diabetic neuropathic pain: A systematic review and meta-analysis

Xintong Li [a], Yang Liu [b], Zheng Jing [b], Baozhu Fan [c], Weimin Pan [d], Shigang Mao [a,*], Yabing Han [e,*]

[a] Department of Rehabilitation Medicine, Qingdao Hospital, University of Health and Rehabilitation Sciences (Qingdao Municipal Hospital), Qingdao, China
[b] Medical College, Sias University, Zhengzhou, China
[c] Department of Medical Laboratory, Qingdao West Coast New Area Central Hospital, Qingdao, China
[d] College of Sports and Health Sciences, Xi'an Physical Education University, Xi'an, China
[e] Medical College, Ankang University, Ankang, China

ARTICLE INFO

Keywords:
Acupuncture therapy
Diabetic neuropathic pain
Diabetes
Systematic review
Meta-analysis

ABSTRACT

Objective: To evaluate the effectiveness of acupuncture in relieving diabetic neuropathic pain and to establish a more reliable and efficient foundation for acupuncture practice in diabetes care.

Methods: The Chinese National Knowledge Infrastructure, Wanfang database, Chongqing Weipu, Chinese Biomedical Literature Database, PubMed, Embase, and Cochrane Library were all searched for a randomized controlled trial research of acupuncture for DNP. Two researchers independently performed literature screening, quality evaluation, and data extraction. After selecting studies and extracting data, we conducted the data analysis using RevMan 5.4 and Stata 14.0. The quality was assessed using the Cochrane Risk of Bias Assessment Tool.

Results: An extensive review of 19 studies involving 1276 patients up to April 29, 2023, found that acupuncture was successful in improving pain intensity [MD= −1.09; 95% CI (−1.28, −0.89), $P < 0.00001$], clinical efficacy indicating pain changes [RR= 1.22; 95% CI (1.15, 1.29), $P < 0.00001$], and clinical neuropathy [MD= −1.55; 95% CI (−3.00, −0.09), $P = 0.04$] in DNP patients. Quality of life was also improved, with few side effects reported.

Conclusion: According to this meta-analysis, acupuncture therapy significantly improved the clinical efficacy of pain intensity, pain changes, and clinical neuropathy in patients with DNP, improved the quality of life of patients to a certain extent, and had lower side effects. This discovery provides evidence-based and practical recommendations for the treatment of DNP patients.

1. Introduction

The prevalence of diabetes has increased dramatically worldwide, with approximately 415 million people worldwide currently living with diabetes, and it is expected to increase to 629 million by 2045.[1,2] Diabetic neuropathic pain (DNP) is a common complication of diabetes, affecting one-third of diabetic patients, with intermittent or continuous pain, allodynia, and hyperalgesia (evoked pain) as the primary clinical features, mainly in the distal limbs, with a symmetrical distribution.[3,4] And DNP has been linked to issues with sleeping, impaired daily functioning, heightened levels of anxiety and depression, decreased efficiency, poor health-related quality of life, and a heightened economic strain.[5,6]

The etiology of DNP remains obscure and is suspected to be the consequence of a multifaceted amalgamation of environmental and genetic elements, blood glucose levels, metabolic disorders, vascular trauma or impairment, and psychosocial factors.[7–9]As a result, the treatment of DNP is challenging due to its chronic and multi-etiological nature. Conventional treatment is pharmacological, primarily in order to achieve pain relief, glycemic control, nerve nutrition, and improvement of microcirculation and metabolic disorders.[10] However, pharmacological treatment has been questioned, involving uncertain drug effects, more side effects, susceptibility to drug resistance or adverse drug reactions, and difficulty in long-term pain control and clinical

* Corresponding authors.
E-mail addresses: maoshigang@163.com (S. Mao), hyb1532589001@163.com (Y. Han).

https://doi.org/10.1016/j.ctim.2023.102992
Received 25 June 2023; Received in revised form 10 September 2023; Accepted 2 October 2023
Available online 5 October 2023

neuropathy improvement.[11,12] Thus, there is an urgent need for patients with DNP to find a safe and effective non-pharmacological therapy for a breakthrough.

In recent years, acupuncture therapy has gained popularity in treating numerous types of pain. Its therapeutic mechanisms may involve alleviating peripheral or central sensitization, regulating ion channel expression, modulating cell signaling pathways, regulating pain-related receptor expression, and inhibiting glial cell activation.[13–15] Some studies[16,17] have shown that acupuncture therapy can improve symptoms such as numbness, pain, and superficial sensory disorders in the extremities of patients with DNP. It is easy to operate and has few side effects, with broad clinical application prospects and essential research value. Although there are an increasing number of published studies on improving DNP through acupuncture therapy, there needs to be more consensus. Its effectiveness and safety are still controversial, and a systematic review and meta-analysis are needed to determine the exact efficacy of acupuncture therapy on DNP. This systematic review and meta-analysis examined the impact of acupuncture therapy on individuals with DNP, intending to provide a fresh, evidence-based approach to treating DNP patients.

2. Materials and methods

This meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration to ensure data quality. The study was prospectively registered in PROSPERO, and the registration number was CRD42023415528.

2.1. Inclusion criteria

2.1.1. Type of participants

Participants with type 1 or type 2 diabetes, aged 18 years or older, were diagnosed with DNP. This study did not restrict the subjects in terms of gender, educational background, place of residence, or disease duration.

2.1.2. Type of interventions

In the experimental group, acupuncture was used either as a monotherapy or an adjunctive therapy in combination with other therapeutic interventions. Acupuncture was the stimulation of body tissues along specific pathways or meridians. The control group received no intervention or other active treatments, such as sham acupuncture, medications, and conventional treatments.

2.1.3. Type of outcome measures

The primary outcome measure was pain intensity, assessed with a visual analog scale (VAS), and other scales were excluded. Clinical efficacy indicating pain improvement, clinical neuropathy, quality of life, and adverse events were all considered secondary indicators.

2.1.4. Types of studies

Randomized controlled trial (RCT), language restricted to Chinese or English.

2.2. Exclusion criteria

(1) Animal experiments;
(2) Studies using laser acupuncture, hydro-acupuncture, or moxibustion alone as interventions to stimulate acupuncture points;
(3) Studies missing critical data, which cannot be extracted or obtained;
(4) Studies on repeated publication of the same experimental data;
(5) Studies that were cohort studies, case reports, or review articles.

2.3. Literature search strategy

Two researchers conducted individual inquiries of the China Knowledge Network (CNKI), Wanfang database, Chongqing Weipu (VIP), China Biomedical Literature Database (CBM), PubMed, Embase, and Cochrane Library from the date of establishment until April 29, 2023. For instance, Pubmed was searched using the strategy detailed in Appendix 1. Additionally, manual searches were conducted for trial registration information (China Clinical Trials Register and ClinicalTrials.gov) and references of the included literature for grey literature.

2.4. Literature screening and data extraction

Two independent researchers (XTL and YL) performed literature screening using EndNote X9 and cross-checked at the end. A third researcher (YBH) intervened to arbitrate when disagreements arose. Two independent researchers (ZJ and WMP) extracted data according to pre-established requirements. The data extraction mainly included (1) the first author, year, and country of publication; and (2) baseline characteristics, sample size, interventions and outcome indicators of the experimental group and the control group.

2.5. Evaluation of literature quality

Two investigators (XTL and BZF) independently evaluated the risk of Bias of RCTs using the Cochrane Collaboration Network's Risk of Bias Assessment Tool 1.0.[18] A third investigator (SGM) intervened when there was disagreement in the evaluation. Six domains of bias were evaluated: random sequence generation, allocation concealment, blinding, incomplete data reporting, selective reporting, and other sources of bias. All individual studies and their respective domains were evaluated and rated as "low risk," "unclear risk," or "high risk." If the number of experiments taken into account exceeded 10, funnel plots were used to check for publication bias.

2.6. Synthesizing and examining data

The meta-analysis was conducted using RevMan 5.4 and Stata 14.0. The effect size for the continuous data was represented by the mean difference (MD). Otherwise, the standardized mean difference (SMD) was used, and in both cases, 95% confidence intervals (CI) were calculated. Relative risk (RR) was used for dichotomous data with 95%CI. The Chi-square and I^2 tests were employed to assess statistical heterogeneity. When the heterogeneity test indicated that the data was not significantly different ($P > 0.1$, $I^2 < 50\%$), the fixed effect model was applied. If the differences between studies were significant ($P \leq 0.1$, $I^2 \geq 50\%$), we utilized a random effects model (REM), and subgroup analysis and sensitivity analysis were performed to identify the source of variation. If meta-analysis were not feasible, we would perform a descriptive analysis instead.

3. Results

3.1. Study selection

A total of 1775 related articles were obtained. After eliminating 779 duplicate entries, a tally of 19 relevant articles[19–37] were finally included according to the inclusion and exclusion criteria. A graphical representation of the literature screening process and its outcomes is provided in Fig. 1.

3.2. Characteristics of the included studies

Nineteen studies were considered from the inception of the databases until April 29, 2023. They included one from the United States, one from

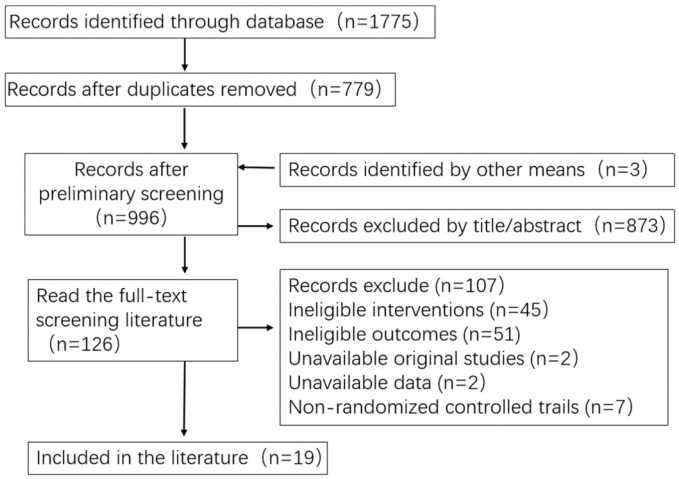

Fig. 1. Flow diagram of literature screening.

the United Kingdom, and the remaining seventeen from China. The number of participants in each study varied from 34 to 96 people. The meta-analysis was conducted on a sample of 1276 individuals, of which 641 were in the experimental group and 628 were in the control group. The essential findings of these studies are outlined in Appendix 2.

3.3. Quality assessment

This analysis included nineteen randomized controlled trials (RCTs), all of which had rigorous subject selection criteria. Thirteen studies[19–21,23,25–27,29,31,33–35,37] explained the process of random sequence generation, while five of these[19–21,23,31] provided a comprehensive overview of allocation concealment. The only study[22] to employ a sham device therapy as the control group ensured that both participants and those administering the treatment were kept unaware of the specifics of the intervention. Cheng et al.[20] and Xu et al.[29] had a minimal risk of bias in assessing the results. All studies produced total outcomes. Six studies[19,23–25,30,37] had a low probability of selective reporting bias. The study of Gao et al.[22] had a high risk of other bias due to a significant difference in the mean disease duration at the baseline data. The quality of the literature is assessed in Figs. 2 and 3.

3.4. Results of meta-analysis

3.4.1. Pain intensity

The research on the efficacy of acupuncture therapy in relieving the pain of DNP was based on seven studies[21,23,26,27,32,33,35] that included a total of 473 participants and employed VAS scores (0–10 cm scale) as the measure of pain intensity. The results revealed heterogeneity among the outcome indicators ($P = 0.08$, $I^2 = 47\%$), and thus, the random-effects model was selected. The meta-analysis showed that the experimental group significantly improved VAS scores compared to the control group (MD = −1.14; 95% CI −1.44 to −0.84), as illustrated in Fig. 4.

3.4.1.1. Acupuncture therapy plus basic treatment vs. basic treatment. Analysis of the data collected from Yang and Kong[32] and Yang et al.[33] revealed that the VAS scores were significantly lower for the acupuncture plus basic treatment group compared to the basic treatment group alone (MD = −1.45; 95% CI −2.39 to −0.51) (Fig. 5A).

3.4.1.2. Acupuncture plus medicine vs. medicine. The results of the meta-analysis of two studies[26,27] demonstrated that the VAS was significantly reduced in the acupuncture plus medication group compared to the medication group (MD = −0.99; 95% CI −1.25 to −0.74) (Fig. 5B).

3.4.2. Clinical efficacy indicating pain improvement

Studies conducted between 2003 and 2022, involving a total of 1124 participants, have shown that acupuncture is a successful treatment for DNP, with the total effective rate of pain improvement being determined through the analyses of 16 studies.[20–22,24–32,34–37] Our results showed that there was no heterogeneity among the outcome indicators ($P = 0.29$, $I^2 = 14\%$), so the fixed effect model was selected. The results of the meta-analysis, displayed in Fig. 6, showed that the experimental group had a significantly greater total effective rate than the control group (RR = 1.22; 95% CI 1.15–1.29).

3.4.2.1. Acupuncture therapy plus basic treatment vs. basic treatment. The overall effective rate was more significant in the acupuncture plus basic treatment group than in the basic treatment group, according to a meta-analysis of three studies (RR=1.18; 95% CI 1.05–1.32) (Fig. 7A).[22,28,30,32]

3.4.2.2. Acupuncture plus medicine vs. medicine. The total effective rate was higher in the acupuncture plus medicine group than in the medicine group (RR=1.33; 95% CI 1.18–1.50), according to the results of a meta-analysis of five studies (Fig. 7B).[25–27,30,36]

3.4.2.3. Acupuncture plus medicine and basic treatment vs. medicine plus basic treatment. The overall effective rate was higher in the acupuncture plus medication and basic treatment group than in the medication plus primary treatment group (RR=1.21; 95% CI 1.10–1.35), according to the results of a meta-analysis of five studies (Fig. 7C).[24,31,34,35,37]

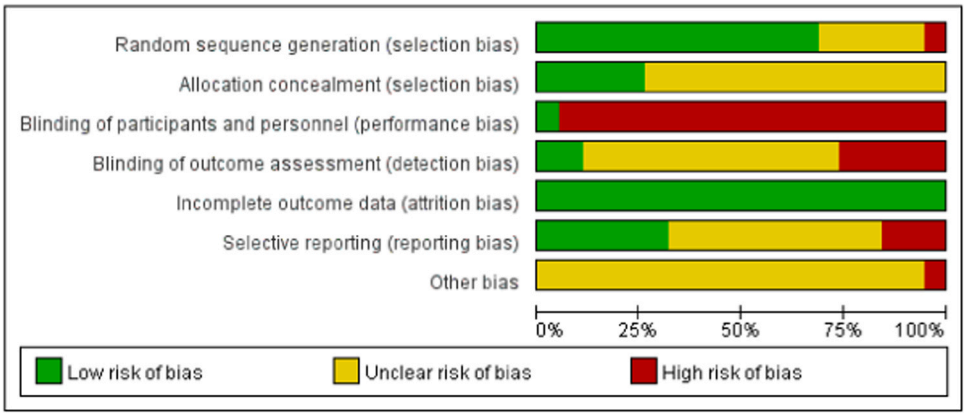

Fig. 2. Bias risk assessment of the included studies.

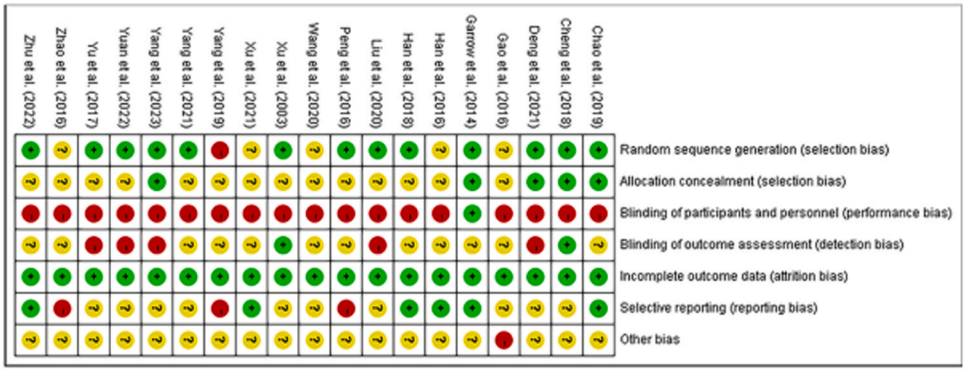

Fig. 3. Summary of bias risks of the included studies.

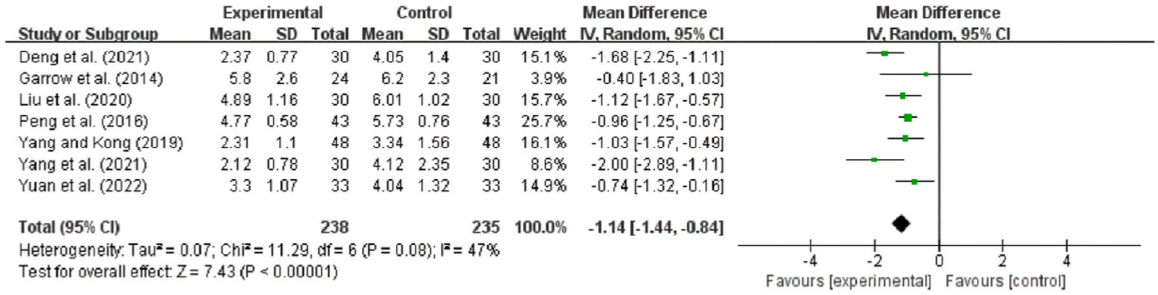

Fig. 4. Forest plot of pain intensity changes.

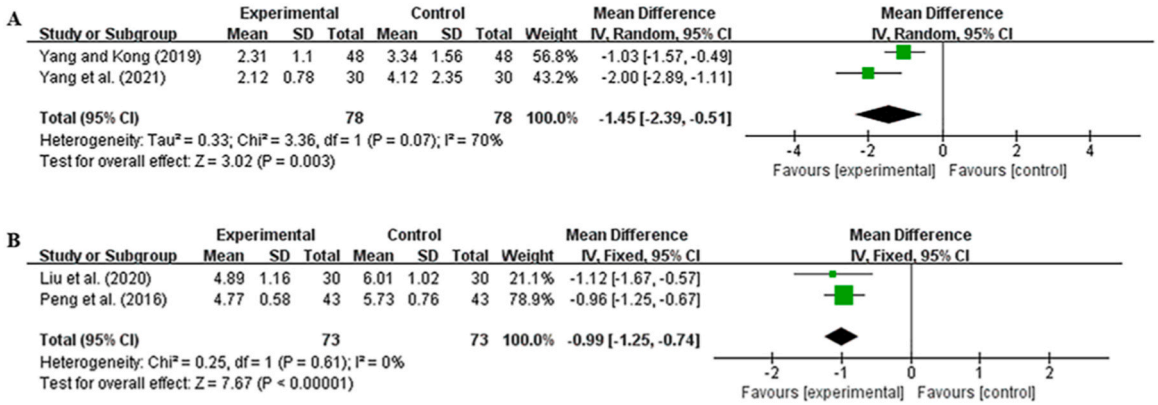

Fig. 5. Forest plot of subgroup analysis of pain intensity changes in different intervention methods.

3.4.3. *Clinical neuropathy*

The Toronto clinical scoring system (TCSS) was utilized in three studies[25,34,35] with 220 participants to evaluate the improvement of clinical neuropathy in DNP treated with acupuncture. The results revealed heterogeneity among the outcome indicators ($P = 0.0008$, $I^2 = 86\%$), and thus, the random-effects model was selected. According to the meta-analysis, the experimental group's TCSS improvement was substantially more significant than the control group's (MD=−1.55; 95% CI −3.00 to −0.09) (Fig. 8). Due to the small number of included studies, sensitivity analysis was used to eliminate the study by Han et al.,[25] which reduced heterogeneity with a 95% CI of − 1.72 to 0.06 but an I^2 of 57%.

3.4.4. *Quality of life*

The Medical Outcomes Study 36-item short-form health survey (SF-36) was used in three trials with 139 individuals to measure the quality of life in DNP treated with acupuncture. According to Deng et al.,[21] the experimental and control groups' post-treatment physical functioning (PF), role-physical (RP), general health (GH), bodily pain (BP), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH) scores improved compared to pre-treatment ($P < 0.05$) and were higher in the experimental group than in the control group ($P < 0.05$). According to Garrow et al.,[23] the active acupuncture group's BP and physical component scores improved in Comparison to the sham group. In research by Wang et al.,[28] it was also shown that acupuncture combined with essential therapy considerably outperformed basal treatment in terms of increasing patients' SF-36 ratings ($P < 0.05$). Additionally, one study[19] found that patients in the acupuncture treatment group experienced an improvement in their Norfolk quality of life questionnaire–diabetic neuropathy (QOL-DN) scores, which measures the quality of life (baseline to week 12 difference, 11.79, 95% CI 1.92–21.66); however, this improvement was not statistically significant compared to the usual care group (25.58, 95% CI 3.90–55.06).

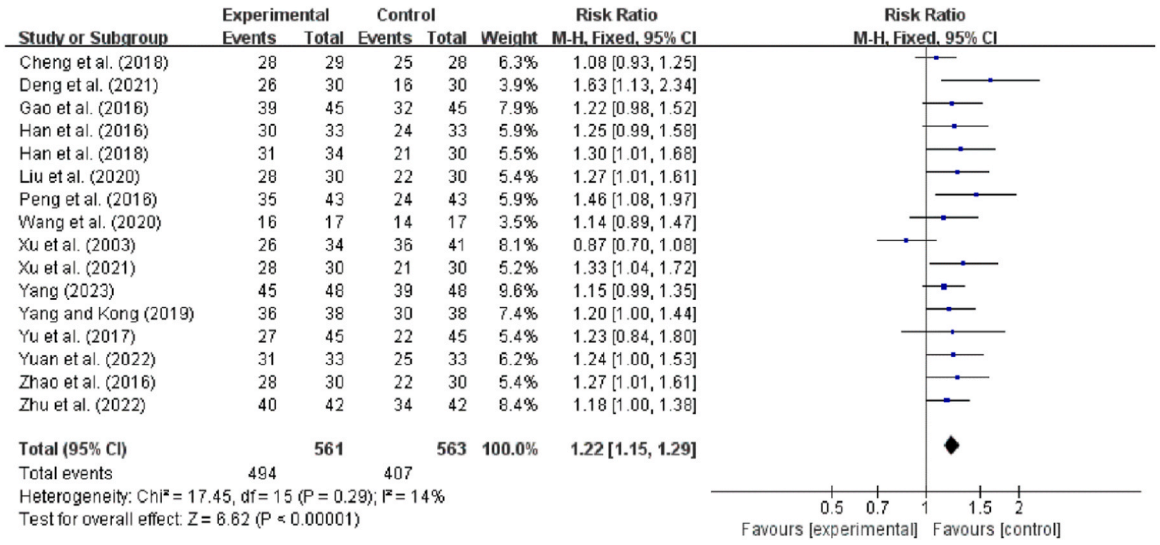

Fig. 6. Forest plot of clinical efficacy indicating pain improvement.

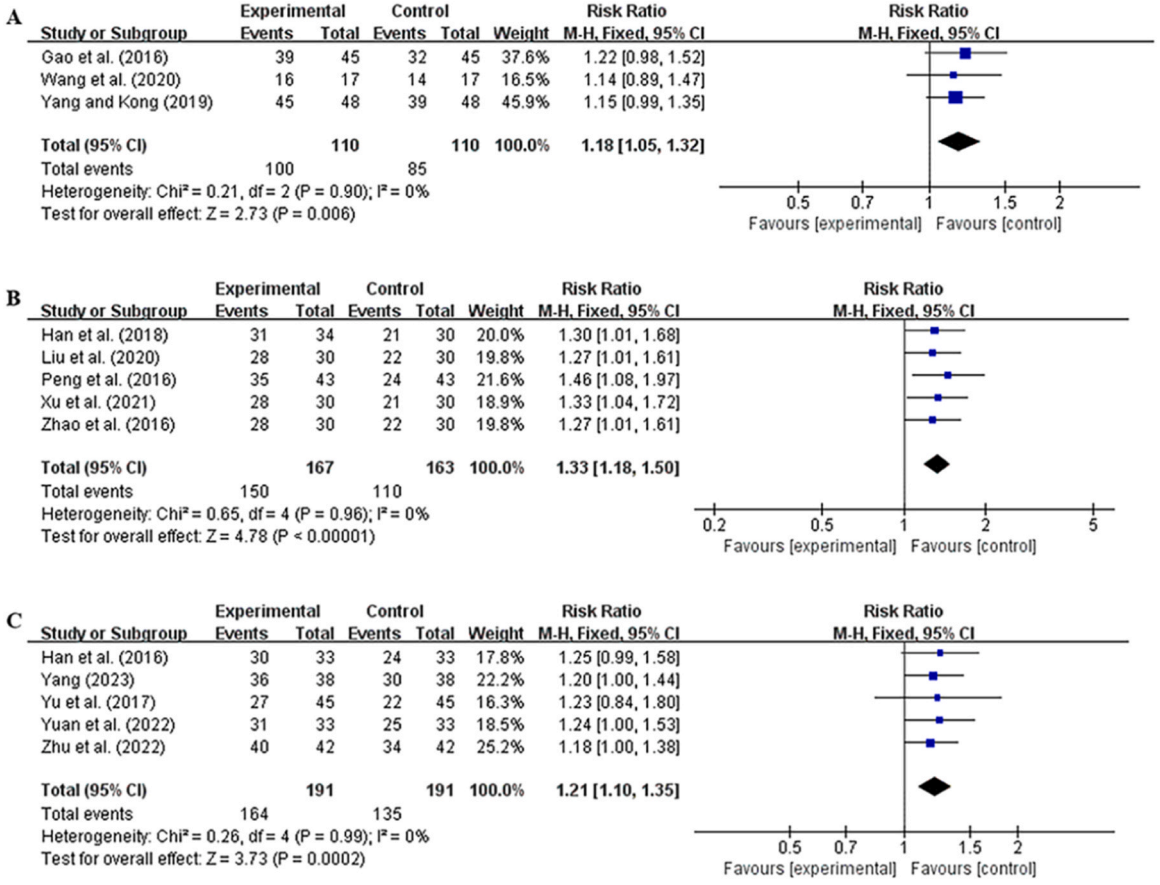

Fig. 7. Forest plot of subgroup analysis of clinical efficacy indicating pain improvement in different intervention methods.

3.4.5. *Adverse events*

Only seven studies[19,20,23,27,30,35,37] offered details on adverse events. According to Chao et al.,[19] the experimental group had side effects from the medication, such as palpitations, cramps, nausea, numbness, swelling, and discomfort in the left arm. One instance of nausea and one case of diarrhea were recorded by Zhu et al.[37] in the experimental group, while two cases of nausea and two cases of diarrhea were observed in the control group. In five trials, no adverse events were recorded in the experimental group.[20,23,27,30,35]

3.4.6. *Publication bias*

With clinical efficacy serving as the outcome indicator, the funnel plot and Egger test of the available literature revealed an asymmetric funnel plot and Egger test, $P = 0.034$, indicating potential Bias, as shown in Fig. 9.

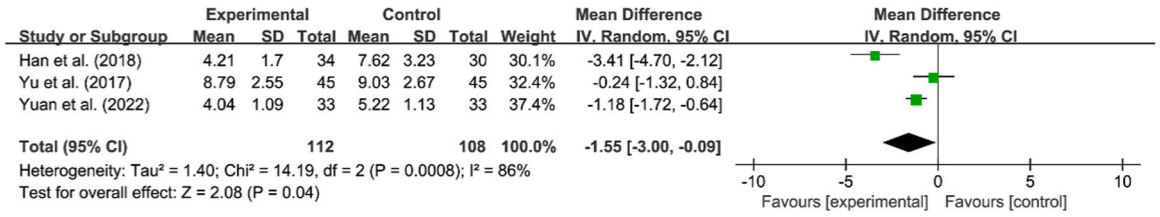

Fig. 8. Forest plot of clinical neuropathy.

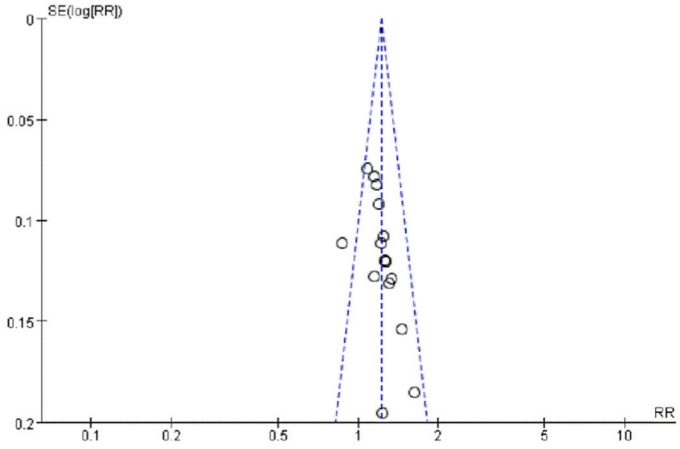

Fig. 9. Funnel plot of publication bias of clinical efficacy.

4. Discussion

4.1. Summary of evidence and analysis

This study examined the effects of acupuncture therapy on DNP using 19 RCTs and 1276 participants. In terms of reducing pain and improving clinical outcomes such as changes in pain, clinical neuropathy, and quality of life, acupuncture therapy alone or in conjunction with other therapies proved superior to controls, with commonly used acupuncture points were Zusanli (ST36), Sanyinjiao (SP6) and Hegu (LI4). This study also reviewed the safety of acupuncture therapy. At the same time, it was being used, revealing that there were very few instances of significant adverse effects and no occurrences of serious adverse events related to acupuncture therapy.

In clinical practice, the analgesic efficacy of acupuncture therapy is generally acknowledged. According to traditional Chinese medicine, excessive thirst and frequent urination (long-term "xiaoke") cause a qi and yin shortage and obstruct the passage of qi and blood to the extremities, which is the cause of diabetic neuropathic pain.[20] Pathological byproducts, including phlegm, blood stasis, and moisture, build up throughout the disease, causing yin deficiency as the underlying cause and dry heat as the expression. The treatment's guiding principles include qi augmentation, yin nourishment, yang warming, phlegm resolution, blood activation, and meridian unblocking. According to Patil et al.,[38] acupuncture therapy has the twin qualities of specificity and integrity. It serves to supplement qi, activate blood circulation, balance yin and yang, unblock meridians, and facilitate the movement of qi and blood to the extremities.

Recent modern medical research has also extensively examined the processes behind the beneficial therapeutic impact of acupuncture on DNP. DNP is primarily due to inflammation, and changes in the levels of pro-inflammatory-related factors like tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), C-reactive protein (CRP), arachidonic acid (AA) derivatives, and others can cause pain and slow down nerve conduction over time.[2] DNP may be successfully treated by inhibiting the inflammatory response and preventing the cascade amplification of its signaling mechanism.[39] Inflammatory factors' ability to enter peripheral nerve tissue is decreased, mechanical and thermal pain sensitivity is decreased, and serum TNF-α is decreased.[40] Additionally, acupuncture has been shown to suppress 12/15 lipoxygenase, which lessens the neuroinflammatory response and delays the onset of DNP,[41] as well as lower patient high sensitivity CRP levels.[42]

Acupuncture therapy has also been demonstrated to assist in controlling endoplasmic reticulum stress (ERS) and reactive oxygen species (ROS). According to research, electroacupuncture dramatically raised mechanical pain thresholds, decreased fasting blood sugar, attenuated oxidative phosphorylation damage, attenuated cell damage, and even prevented death in DNP rats.[17] Acupuncture therapy of DNP rats decreased the expression of GRP78, one of the first endoplasmic reticulum chaperone proteins, decreased the rate of sciatic nerve cell death, safeguarded sciatic nerve tissues, and alleviated DNP-related symptoms, according to Pan et al.[43]

Most of the trials that used acupuncture therapy also used primary or pharmacological treatments involving glucose control. The cause of this might be related to the idea that DNP is impacted by impaired glucose metabolism, as well as the interaction of several mechanisms, including peripheral sensitization, central sensitization, dysfunctional neural mechanisms of upstream and downstream regulation, and changes in ion channels.[44–47] Due to the difficulty in achieving effective pain relief or a "pain-free" state caused by poor glucose metabolism, multidimensional or multiform combination treatment is employed in clinical practice and may be able to demonstrate clinical effectiveness fully. Overall, multiple researches have demonstrated that acupuncture therapy has the potential to be an efficient method for enhancing DNP.

4.2. Recommendations for more study

The next step for researchers should be identifying the ideal acupuncture protocol, including acupuncture form, point selection, acupuncture depth, and treatment frequency, given that DNP patients may have poor resistance and challenging wound healing. Neurography is a very good means of diagnosing and assessing neuropathy, but unfortunately, we did not see this indicator in the included articles, and look forward to more studies using this indicator in the future, and recommend the design of scientific and reasonable clinical protocols, the inclusion of intuitive and accurate quantifiable outcome parameters, the development of larger-scale and high-quality randomized controlled trials (RCTs), and attention to the reporting of negative results to further verify the short-term and long-term efficacy of acupuncture in the treatment of DNP. Acupuncture mechanisms for DNP should also be highlighted, and more research should be done from a multifaceted, interdisciplinary approach and used in clinical settings.

4.3. Strengths and limitations

Our comprehensive review and meta-analysis encompassed the most up-to-date data. They conducted a subgroup assessment based on treatments, furnishing additional evidence-based medical guidance for the future of acupuncture for DNP. Furthermore, acupuncture treatment was distinguished from other forms of treatment, such as fire needling, acupuncture, acupoint application, acupoint injection, and moxibustion,

thereby augmenting the accuracy of the findings. Despite our efforts, the scope of this research was limited as only Chinese and English databases were consulted; other languages were not included. (2) The quality of the literature included needed to meet the necessary standards. The lack of clarity regarding the randomization process, allocation concealment, and blinding in certain studies could give rise to a selection bias and performance bias. (3) The variations in treatments, controls, and endpoints across studies partially impacted the assessment of the efficacy of acupuncture for DNP. It is essential to address these limitations in future research, and it is hoped that scientists will create more effective randomized controlled trials to bolster the previous outcomes.

5. Conclusion

In conclusion, acupuncture therapy improves pain intensity, and clinical efficacy indicating pain changes and clinical neuropathy considerably in patients with DNP, and somewhat enhances their quality of life. However, due to the heterogeneity between the outcome indicators of clinical neuropathy, it is necessary to design additional studies using a rigorous methodology. In addition, acupuncture therapy has the benefits of being safe, practical, and cost-effective and should be promoted further.

Funding

None.

CRedit authorship contribution statement

All authors were involved in the initiation and design of the study. YBH, SGM, XTL, YL and WMP contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by XTL and YL under the supervision of YBH and SGM. The first draft of the manuscript was written by XTL, YBH, ZJ and BZF. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix 1. Search strategy for PubMed

Number	Search terms
#1	"Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh]
#2	"Acupuncture Treatment"[Title/Abstract] OR "Acupuncture Treatments"[Title/Abstract] OR "Treatment, Acupuncture"[Title/Abstract]OR "Therapy, Acupuncture"[Title/Abstract] OR "Pharmacoacupuncture Treatment"[Title/Abstract] OR "Treatment, Pharmacoacupuncture"[Title/Abstract] OR "Pharmacoacupuncture Therapy"[Title/Abstract] OR "Therapy, Pharmacoacupuncture"[Title/Abstract] OR "Acupotomy"[Title/Abstract] OR "Acupotomies" [Title/Abstract] OR "Pharmacopuncture"[Title/Abstract]
#3	#1 OR #2
#4	"Diabetic Neuropathies"[Mesh]
#5	"Diabetic Neuropathy"[Title/Abstract]) OR "Neuropathies, Diabetic"[Title/Abstract] OR "Neuropathy, Diabetic"[Title/Abstract] OR "Diabetic Autonomic Neuropathy"[Title/Abstract] OR "Autonomic Neuropathies, Diabetic"[Title/Abstract] OR "Autonomic Neuropathy, Diabetic"[Title/Abstract] OR "Diabetic Autonomic Neuropathies"[Title/Abstract] OR "Neuropathies, Diabetic Autonomic"[Title/Abstract] OR "Neuropathy, Diabetic Autonomic"[Title/Abstract] OR "Diabetic Neuralgia"[Title/Abstract] OR "Diabetic Neuralgias"[Title/Abstract] OR "Neuralgias, Diabetic"[Title/Abstract] OR "Diabetic Neuropathy, Painful"[Title/Abstract] OR "Neuropathy, Painful Diabetic"[Title/Abstract] OR "Painful Diabetic Neuropathy"[Title/Abstract] OR "DNP"[Title/Abstract] OR "Diabetic Mononeuropathy"[Title/Abstract]
#6	#4 OR #5
#7	"randomized controlled trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract]
#8	#3 AND #6 AND #7

Appendix 2. Characteristics of included studies

References	Country	Sample size (E/C)	Age (y)	Gender (F/M)	Duration of diabetes (y)	Intervention		Acupoint selections	Intervention duration	Outcomes
						E	C			
Chao et al. (2019)	United States	26/14	E: 58.40 ± 10.60 C: 60.70 ± 11.80	E: 14/12 C: 6/6	/	Acupuncture (1–2 sessions /week, 20–40 min/session) +usual care	Usual care	SP9, GB34, LI11, LU6, ST44, SP10, LI4, LR3, SJ5, GB41, PC6, LU7, KI6, ST36, KI3, SP6, SP3, etc.	12 weeks	QOL-DN
Cheng et al. (2018)	China	29/28	E: 59.45 ± 5.93 C: 61.36 ± 6.68	E: 19/10 C: 16/12	/	Acupuncture (2 sessions /week, 30 min/session) +basic treatment	Superticial acupuncture at sham acupoints +basic treatment	GB34, ST36, KI3, EX-UE9, EX-LE10, etc.	8 weeks	Total effective rate
Deng et al. (2021)	China	30/30	E: 59.00 ± 9.00 C: 57.00 ± 9.00	E: 12/18 C: 15/15	E: 10.40 ± 3.90 C: 9.30 ± 3.60	Acupuncture (1 session/day, 30 min/session) +basic treatment	Pregabalin capsule +basic treatment	SP6, ST36, SP9, SP10, etc.	4 weeks	Total effective rate, VAS, SF-36

(continued on next page)

(*continued*)

Gao et al. (2016)	China	45/45	E: 61.53 ± 7.58 C: 62.13 ± 6.42	E: 17/28 C: 18/27	E: 1.5–11 C: 1.5–10	Acupuncture (5 sessions /week, 20–30 min/session) +basic treatment	Basic treatment	LI15, LI11, SJ5, LI4, GB34, ST36, LR3, ST41, etc.	40 days	Total effective rate
Garrow et al. (2014)	UK	24/21	E: 68.00 ± 11.10 C: 63.00 ± 10.80	E: 8/16 C: 6/15	E: 12.20 ± 7.40 C: 11.00 ± 9.20	Acupuncture (10 sessions /week, 30 min/session)	Sham acupuncture	LR3, KI3, SP6, SP10, ST36, etc.	10 weeks	VAS, SF-36
Han et al. (2016)	China	33/33	E: 63.10 ± 6.20 C: 63.80 ± 5.90	E: 15/18 C: 16/17	E: 8.10 ± 2.60 C: 7.80 ± 3.10	Acupuncture (every two days, 30 min/session) +mecobalamin +basic treatment	Mecobalamin +basic treatment	KI3, SP6, ST36, GB34, LI4, LR3, BL23, BL18, BL13, BL20, etc.	60 days	Total effective rate
Han et al. (2018)	China	34/30	E: 66.90 ± 3.60 C: 65.60 ± 4.70	E: 12/22 C: 11/19	E: 4–11 C: 3–12	Acupuncture (5 sessions /week, 30 min/session) +Acupoint injection of mecobalamin	Acupoint injection of mecobalamin	LI4, SJ5, LI11, ST36, BL40, SP9, SP6, KI3, LR3, etc.	4 weeks	Total effective rate, TCSS
Liu et al. (2020)	China	30/30	E: 61.36 + 3.08 C: 61.89 ± 3.57	E: 17/13 C: 15/15	E: 6.98 ± 1.85 C: 7.68 ± 1.24	Acupuncture (45 min/session) +hypoglycemic drugs	Hypoglycemic drugs	SJ3, SJ4, LI4, LI5, SI3, KI3, KI6, BL62, SP6, etc.	4 weeks	Total effective rate, VAS
Peng et al. (2016)	China	43/43	E: 56.39 ± 4.63 C: 57.52 ± 5.26	E: 16/27 C: 18/25	E: 1.15 ± 0.41 C: 1.23 ± 0.32	Acupuncture (1 session/day, 20–30 min/session) +gliclazide +mecobalamin	Gliclazide +mecobalamin	RN4, BL23, RN13, EX-B3, ST36, SP6, LI11, LI4, etc.	30 days	Total effective rate, VAS
Wang et al. (2020)	China	17/17	E: 61.05 ± 3.84 C: 60.28 ± 4.49	E: 6/11 C: 7/10	E: 4.59 ± 1.16 C: 4.15 ± 2.03	Acupuncture (every two days, 30 min/session) +basic treatment	Basic treatment	RN6, ST36, SP6, BL60, RN4, etc.	12 weeks	Total effective rate, SF-36
Xu et al. (2003)	China	34/41	E: 53.62 ± 11.17 C: 54.98 ± 12.03	E: 19/15 C: 21/20	/	Acupuncture (every two days, 30 min/session) +basic treatment	Basic treatment + tapping collaterals	EX-B3, ST36, LI11, EX-LE10, EX-UE9, etc.	40 days	Total effective rate
Xu et al. (2021)	China	30/30	E: 47. 58 ± 4.16 C: 47. 12 ± 5.12	E: 12/18 C: 14/16	E: 9. 19 ± 4. 46 C: 9. 25 ± 5. 03	Acupuncture (1 session/day, 40 min/session) +Mecobalamin	Mecobalamin	LI4, SJ5, LI11, LI15, GB34, SP6, GB30, GB39, etc.	12 weeks	Total effective rate
Yang (2023)	China	38/38	E: 56.36 ± 6.68 C: 56.72 ± 6.54	E: 16/22 C: 18/20	E: 6.20 ± 1.79 C: 6.18 ± 1.84	Acupuncture (30 min/session) +epalrestat +basic treatment	Epalrestat+ basic treatment	BL20, SP10, RN4, BL18, BL23, SP6, RN6, etc.	36 days	Total effective rate
Yang and Kong (2019)	China	48/48	/	E: 21/27 C: 23/25	/	Acupuncture (1 min/acupoint) +basic treatment	Basic treatment	/	4 weeks	Total effective rate, VAS
Yang et al. (2021)	China	30/30	E: 71.23 ± 4.35 C: 72.15 ± 5.13	E: 16/14 C: 15/15	/	Acupuncture (1 session/day, 30 min/session) +basic treatment	Basic treatment	SJ5, LI11, LI4, SP6, LR3, ST36, etc.	4 weeks	VAS
Yu et al. (2017)	China	45/45	E: 60–69 C: 60–68	E: 20/25 C: 24/21	/	Acupuncture (30 min/session) +Mecobalamin +basic treatment	Mecobalamin +basic treatment	LI13, LI11, SJ5, LI4, ST36, SP6, GB34, KI3, etc.	4 weeks	Total effective rate, TCSS
Yuan et al. (2022)	China	33/33	E: 55.88 ± 7.98 C: 53.45 ± 9.44	E: 16/17 C: 15/18	E: 9.35 ± 2.03 C: 9.46 ± 1.75	Acupuncture (1 session/day, 30 min/session) +Qigui Huoxue Decoction +basic treatment	Qigui Huoxue Decoction +Basic treatment	EX-LE10, EX-UE9, LR3, SP6, ST36, PC6, etc.	4 weeks	Total effective rate, TCSS, VAS
Zhao et al. (2016)	China	30/30	53.00 ± 9.20	25/35	/	Acupuncture (1 session/day, 30 min/session) +methylcobalamin +nimodipine	Methylcobalamin +nimodipine	KI6, BL62, SJ5, PC6, LU7, SP4, GB41, SI3, etc.	8 weeks	Total effective rate
Zhu et al. (2022)	China	42/42	E: 51.93 ± 2.48 C: 51.89 ± 2.40	E: 12/30 C: 13/29	/	Acupuncture (1 session/day, 30 min/session) +mecobalamin +basic treatment	Mecobalamin +basic treatment	PC6, ST36, RN6, LI4, SP10, BL13, SP6, EX-B3, etc.	4 weeks	Total effective rate

E, experimental group; C, control group; y, years; min, minutes; F, female; M, male; VAS, visual analogue scale; TCSS, Toronto clinical scoring system; QOL-DN, the Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; SF-36, the Medical Outcomes Study 36-item short-form health survey

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