Lower Extremity Nerve Decompression for Diabetic Peripheral Neuropathy: A Systematic Review and Meta-analysis

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Background: Diabetic peripheral neuropathy (DPN) is a leading cause of morbidity. This systematic review and meta-analysis evaluate the efficacy of lower extremity nerve decompression in reducing DPN symptoms and complications.

Methods: A database search was performed using Medline, Embase, Google Scholar, and Cochrane Central Register of Controlled Trials. Articles addressing surgical decompression of lower limb peripheral nerves in patients with diabetes were screened for inclusion. Two independent reviewers undertook the assessment. Methodological quality measures were the Cochrane risk of bias and Newcastle-Ottawa scale.

Results: The pooled sample size from 21 studies was 2169 patients. Meta-analysis of 16 observational studies showed significant improvement in the visual analog scale (VAS) ($P < 0.00001$) and two-point discrimination ($P = 0.003$), with strong reliability. Decompression of the tarsal tunnel region had the highest improvement in VAS [MD, 6.50 (95% CI, 3.56–9.44)]. A significant low-risk ratio (RR) of ulcer development and lower limb amputation was detected ($P < 0.00001$). Lowest RR of ulcer development was detected with tarsal tunnel release [RR, 0.04 (95% CI, 0.00–0.48)]. Improvements in VAS, two-point discrimination, and nerve conduction velocity were nonsignificant in the meta-analysis of five randomized controlled trials (RCTs). The RCT analysis was limited to only two studies for each outcome.

Conclusions: Meta-analysis of observational studies highlights the efficacy of lower extremity nerve decompression in reducing DPN symptoms, ulcerations, and amputations. Releasing the tibial nerve in the tarsal tunnel region was the most effective observed procedure. Nevertheless, high-quality RCTs are required to support the utility of this intervention in DPN. *(Plast Reconstr Surg Glob Open 2022;10:e4478; doi: 10.1097/GOX.0000000000004478; Published online 18 August 2022.)*

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a leading cause of morbidity, affecting nearly half of patients with long-term diabetes. One in every five patients with DPN develops a diabetic foot ulcer, with a recurrence rate of almost 100% within 10 years.[1] DPN typically results in pain, paresthesia, and numbness in the distal lower limbs. Traditional management focuses on lifestyle improvement, near-normoglycemia maintenance, and pharmacotherapy for symptomatic alleviation of pain.[2] Unfortunately, DPN treatment is not always effective. For more than 30 years, peripheral nerve decompression in patients with DPN has been explored as one of the promising treatment options, and multiple studies have shown encouraging results.[3–5] However, this intervention is still not widely offered to patients with DPN, and the evidence behind it warrants additional review. The objective of this systematic review and meta-analysis is to evaluate the effectiveness of surgical decompression of lower extremity peripheral nerves in reducing symptoms and complications related to DPN.

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METHODOLOGY

Protocol and Eligibility Criteria

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[6] The intervention group consisted of adults with DPN who underwent surgical decompression of peripheral nerves in the lower extremity, whereas the control group included patients with a contralateral nonoperated leg or patients with DPN who did not have surgery. The primary outcome of interest of this study was postoperative clinical improvement. This was evaluated by reviewing the pain visual analog scale (VAS) or the two-point discrimination (2PD) sensory test. The secondary outcomes were changes in nerve conduction velocity (NCV), ulcer development, and the need for lower limb amputation. Studies among patients with an established diagnosis of compression neuropathies, in vitro or animal studies, review papers, expert opinions, case reports, and non-English articles were excluded from this systematic review.

Search Strategy and Study Selection

The present systematic review was carried out using Medline, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials. The period covered was from inception to November 1, 2021. The key terms used were "nerve decompression" or "nerve release" or "tunnel release" or "surgical release" or "compression neuropathy" and "diabetes" or "diabetic neuropathy" or "peripheral neuropathy" or "painful neuropathy. The abstracts of all related articles addressing surgical decompression of lower limb peripheral nerves in patients with diabetes were reviewed. The reference lists of articles included in this review and recent related reviews were examined. Relevant articles published in English peer-reviewed journals were selected. Titles and abstracts were screened to assess the eligibility of the identified articles. A full-text review for inclusion and data extraction was done by two independent reviewers (W.A. and T.A.). Interrater reliability was analyzed to confirm agreement. When data or eligibility was in question, this was discussed with the senior author to reach consensus.

Data Extraction

The following data were extracted from each article: author, year of publication, journal, country, study design, mean age, sample size, funding, indication for surgery, type of intervention, control treatment, other comparison treatment, follow-up time, outcome measurement, and results. The extracted data were collected in a structured Excel spreadsheet (Microsoft Corp., Redmond, Wash.).

Statistical Analysis

Statistical analyses were performed with Review Manager Version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark). The Cochrane risk of bias assessment tool was used to assess the methodologic quality of identified randomized-controlled trials (RCTs).[7] The Newcastle-Ottawa scale (NOS) was used to evaluate observational studies,[8]

Takeaways

Question: Can lower extremity nerve decompression reduce symptoms and complications of diabetic peripheral neuropathy (DPN)?

Findings: Meta-analysis of observational studies highlights the efficacy of nerve decompression in reducing DPN symptoms, ulcerations, and amputations. Tibial nerve release in the tarsal tunnel region was the most effective procedure. Randomized controlled trial (RCT) analysis showed nonsignificant improvement following surgery. This analysis of RCTs was limited by high heterogeneity and low number of studies.

Meaning: Success of lower extremity nerve decompression in reducing DPN symptoms and complications is strongly supported by observational studies. Nevertheless, high-quality RCTs are required to support the utility of this intervention in this patient population.

assessing three sections: (1) representativeness of the study population, (2) comparability of cohorts, and (3) evaluation of outcomes (follow-up).

Mean differences and standard errors were calculated using inverse variance to assess VAS and 2PD outcomes. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to evaluate the ulcer development and amputation outcomes, and a P value less than 0.05 was considered statistically significant. The Cochrane $\chi 2$ test was performed to estimate heterogeneity of studies, with a P value less than 0.05 indicating the existence of heterogeneity. To estimate the impact of heterogeneity on the meta-analysis, I^2 values were calculated. I^2 values greater than or equal to 50% and P less than 0.05 indicated a moderate-to-high degree of heterogeneity in pooled articles. A fixed-effects design was used when the I^2 value was less than 50% ($P > 0.05$); otherwise, a random-effects design was adopted.

Egger's test was conducted using Statistical Package for Social Sciences version 25 (IBM Corp., Armonk, N.Y.) to evaluate publication bias, which was further estimated by visual inspection of symmetry in funnel plots. Subgroup and sensitivity analyses were performed for VAS, 2PD, ulcer development, and amputation outcomes in observational studies to determine the robustness of observed outcomes and evaluate likely causes of heterogeneity. The subgroup analysis was not performed for RCT studies, given that the number of articles for each outcome was limited.

RESULTS

Study Selection

The database search identified 250 articles, whereas 16 others were identified through manual review of the selected articles' references (Fig. 1). Following the screening of titles and abstracts from the initial search, 30 articles were selected for full-text review. After the full-text review, nine articles were excluded because they did not satisfy the inclusion criteria or had inappropriate outcome reporting, leaving 21 articles eligible for final inclusion. The included
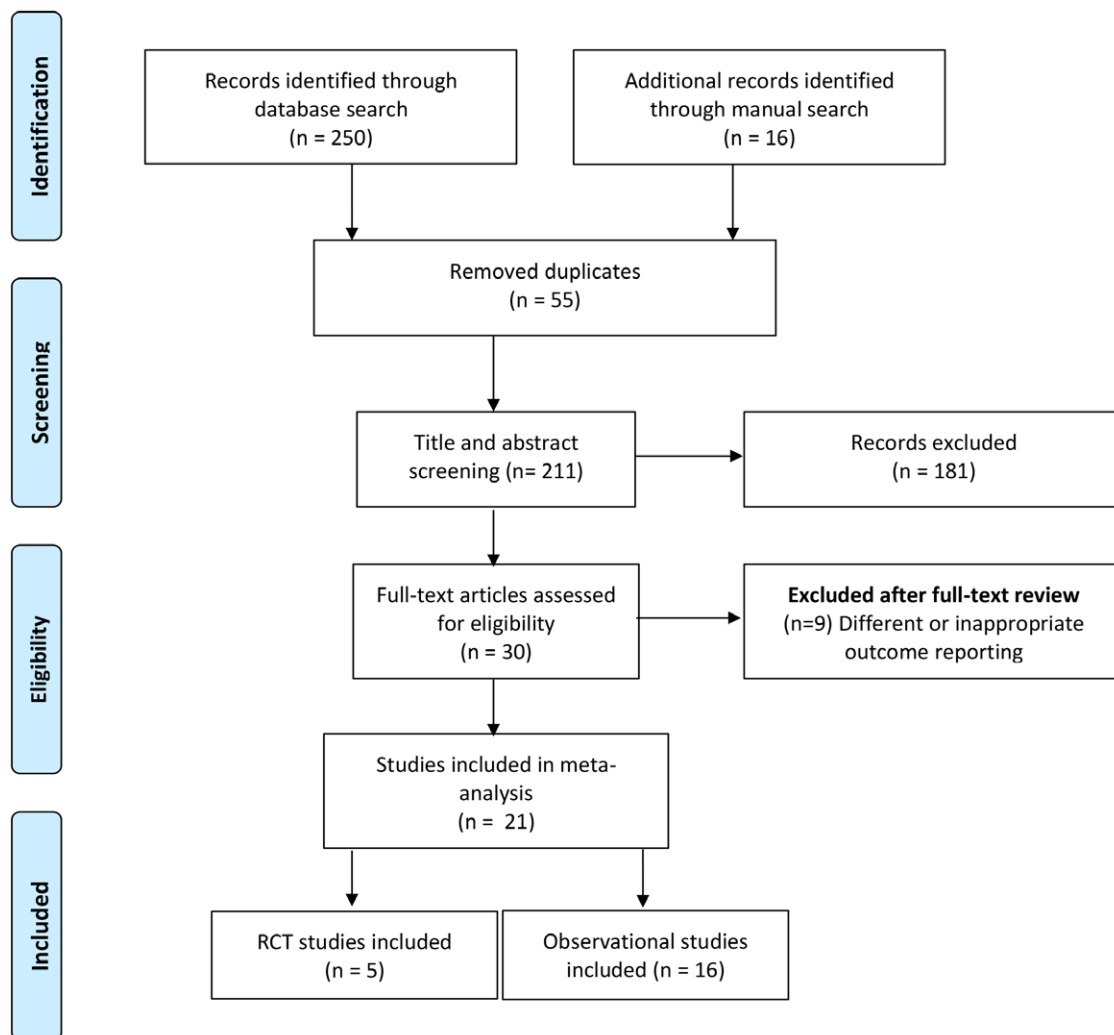
Fig. 1. Study flow diagram.

studies are five RCTs and 16 observational studies.[1,4,9–27] The pooled sample size of patients from all studies was 2169, of which 612 were from RCTs and 1557 from observational studies. The level of evidence of all studies included in this review ranged from levels I to III on the Oxford Center for Evidence-Based Medicine scale.[28] Tables 1–4 summarize the characteristics of these studies.

Quality Assessment and Risk of Bias

The Cochrane risk of bias assessment tool was utilized. All the RCTs included in this review were judged to be at low risk of bias for outcome assessment blinding. A high proportion of the RCTs (75%) mentioned a low risk of bias for randomization, and selective outcome reporting had incomplete outcome data. However, a high risk of bias for allocation concealment was detected in all RCTs. Similarly, more than half of the RCTs were at a high risk of bias for blinding of participants and personnel (Fig. 2). Observational studies were assessed using NOS. All included studies were judged to be at a low risk of bias for the follow-up criteria, and most mentioned a low risk of bias for the representativeness of the study population.

However, a high risk of bias for comparability criteria was detected in 75% of studies because they did not describe a control group (Fig. 3).

To account for bias related to duplicate study effects, publications that appeared to be from one data set were not included in the same analysis. Based on Egger's regression test for RCT studies and the visual examination of the funnel plot, no proof of publication bias was detected for any of the three outcomes analyzed [P (VAS), 0.56; P (2PD), 0.62; P (NCV), 0.87; Fig. 4]. Similarly, no proof of publication bias was detected in observational studies for any of the four outcomes analyzed [P (VAS), 0.08; P (2PD), 0.12; P (ulcer development), 0.06; P (amputation), 0.34; Fig. 5].

ASSESSMENT OF HETEROGENEITY

RCT Studies

VAS Outcome

Two of the five included RCTs reported VAS outcomes. As heterogeneity was high (χ2, 16.87; $P < 0.0001$; I^2, 94%), a random effects model was adopted. Pooled analysis

Table 1. Summary of the Randomized Controlled Trials Included in This Review

Authors	Year	Title	Country	Journal	Intervention	Hoffmann-Tinel Sign	Primary Outcome	Complications
Zhang et al[19]	2013	Evaluation of the clinical efficacy of multiple lower extremity nerve decompression in diabetic peripheral neuropathy	China	JNLS	Common peroneal, deep peroneal, and tarsal tunnel	Yes	NCS	Wound dehiscence (n = 2) and postoperative hemorrhage (n = 1)
van Maurik et al[10]	2014	Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy	The Netherlands	JPRS	Common peroneal, superficial peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Hematoma (n = 1) and wound infection (n = 2)
van Maurik et al[11]	2015 (a)	Nerve conduction studies after decompression in painful diabetic polyneuropathy	The Netherlands	J Clin Neurophysiol	Common peroneal, superficial peroneal, deep peroneal, and tarsal tunnel	Yes	NCS	Hematoma (n = 1) and wound infection (n = 2)
van Maurik et al[12]	2015 (b)	The effect of lower extremity nerve decompression on health-related quality of life and perception of pain in patients with painful diabetic polyneuropathy	The Netherlands	Diabet Med	Common peroneal, superficial peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Hematoma (n = 1) and wound infection (n = 2)
Best et al[13]	2019	Surgical peripheral nerve decompression for the treatment of painful diabetic neuropathy of the foot	Canada	Diabetes Res Clin Pract	Common peroneal, deep peroneal, and tarsal tunnel	No	VAS	Wound infection (n = 1)

Diabet Med, Diabetic Medicine; Diabetes Res Clin Pract, Diabetes Research and Clinical Practice; J Clin Neurophysiol, Journal of Clinical Neurophysiology; JNLS, Journal of Neurological Surgery; JPRS, Journal of Plastic and Reconstructive Surgery; NCS, nerve conduction study.

showed a nonsignificant improvement ($P = 0.52$) in the VAS (mean difference, 1.01; 95% CI, –2.05 to 4.08) after surgery (Fig. 6A).

2PD Outcome

Two of the five included RCTs reported 2PD outcomes. As heterogeneity was high ($\chi2$, 52.32; $P < 0.0001$; I^2, 94%), a random effects model was used. Based on our pooled analysis, the preoperative versus postoperative 2PD changes were not statistically significant (mean difference, 7.28; 95% CI, –3.02 to 17.59; $P = 0.17$; Fig. 6B).

NCV Outcome

Two of the five included RCTs reported NCV outcomes. As heterogeneity was high ($\chi2$, 48.19; $P < 0.00001$; I^2, 98%), a random effects model was adopted. Pooled analysis showed a nonsignificant difference ($P = 0.43$) in NCV (mean difference, –3.90; 95% CI, –13.61 to 5.81) after surgery (Fig. 6C).

Observational Studies

VAS Outcome

Nine of the 25 included observational studies reported VAS outcomes. As heterogeneity was low ($\chi2$, 8.60; P, 0.38; I^2, 7%), a fixed-effects model was adopted. Pooled analysis showed a significant improvement ($P < 0.00001$) on VAS (mean difference, 5.10; 95% CI, 4.04–6.16) after surgery (Fig. 7A).

2PD Outcome

Three of the 25 included observational studies reported 2PD outcomes. As heterogeneity was low ($\chi2$, 0.89; $P = 0.64$; I^2, 0%), a fixed-effects model was adopted. Pooled analysis showed a significant improvement ($P = 0.003$) in 2PD (mean difference, 6.46; 95% CI, 2.22–10.69) after surgery (Fig. 7B).

Ulcer Development

Six of the 25 included observational studies reported the prevalence of ulcer development. As heterogeneity was high ($\chi2$, 59.98; $P < 0.00001$; I^2, 92%), a random-effects model was adopted. The forest plot analysis showed that the risk of ulcer development was significantly low (RR, 0.11; 95% CI, 0.05–0.23; $P < 0.00001$; Fig. 7C).

Amputations

Five of the 25 included observational studies reported amputation prevalence. As heterogeneity was high ($\chi2$, 16.47; $P = 0.002$; I^2, 76%), a random-effects model was adopted. The forest plot analysis showed that amputation was significantly low (RR, 0.01; 95% CI, 0.00–0.09; $P < 0.00001$; Fig. 7D).

Sensitivity Analysis

The outcomes in observational studies did not differ substantially, indicating strong reliability of the meta-analysis. In the leave-one-out sensitivity analysis, the mean difference between VAS and 2PD ranged from 4.89 (95% CI, 3.76–6.03) to 5.93 (95% CI, 4.71–7.15) and from 5.46 (95% CI, 0.74–10.18) to 7.32 (95% CI, 1.48–13.16),

AQ11 **Table 2. Summary of the Observational Studies Included in This Review**

Authors	Year	Title	Country	Journal	Study Type	Intervention	Hoffmann-Tinel Sign	Primary Outcome	Complications
Wiemanand Patel[14]	1995	Treatment of hyperesthetic neuropathic pain in diabetics. Decompression of the tarsal tunnel	USA	Ann Surg	Prospective	Tarsal tunnel	Yes	VAS	Ulceration (n = 1) Superficial wound infection (n = 4) Toe numbness (n = 1)
Wood and Wood[4]	2003	Decompression of peripheral nerves for diabetic neuropathy in the lower extremity	USA	JFAS	Cohort	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Wound dehiscence (n = 4)
Aszmann et al[18]	2004	Changing the natural history of diabetic neuropathy: incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure	USA	Ann Plast Surg	Retrospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	Ulcer or amputation	Not reported
Rader[16]	2005	Surgical decompression in lower extremity diabetic peripheral neuropathy	USA	JAPMA	Prospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Wound dehiscence (n: unknown)
Valdivia et al[15]	2005	Surgical treatment of peripheral neuropathy: outcomes from 100 consecutive decompressions	USA	JAPMA	Prospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Not reported
Siemionow et al[17]	2006	Clinical outcome of peripheral nerve decompression in diabetic and nondiabetic peripheral neuropathy	Poland	Ann Plast Surg	Prospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	2PD	Delayed wound healing (n = 3)
Karagoz et al[23]	2008	Early and late results of nerve decompression procedures in diabetic neuropathy: a series from Turkey	Turkey	J Reconst Microsurg	Cohort	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Wound dehiscence (n = 3)
Dellon et al[24] (a)	2012	Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy	USA	J Reconst Microsurg	Prospective	Tarsal tunnel	Yes	Ulcer or amputation	Ulceration (n = 4) Amputation (n = 1) Feet infections (n = 4)
Dellon et al[25] (b)	2012	A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy	USA	J Reconst Microsurg	Prospective	Tarsal tunnel	Yes	VAS	Not reported
Nickerson and Rader[19]	2013	Low long-term risk of foot ulcer recurrence after nerve decompression in diabetic neuropathy cohort	USA	JAPMA	Retrospective	Common peroneal and tarsal tunnel	Yes	Ulcer or amputation	Ulceration (n = 9) Delayed wound healing (n = 3)
Liao et al[20]	2014	Surgical decompression of painful diabetic peripheral neuropathy: the role of pain distribution	China	PLOS ONE	Retrospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Wound dehiscence (n = 2) Subcutaneous hemorrhage (n = 1)
Anderson et al[29]	2017	Acute improvement in intraoperative EMG following common fibular nerve decompression in patients with symptomatic diabetic sensorimotor peripheral neuropathy: 1. EMG results	USA	JNLS	Retrospective	Common peroneal nerve decompression	Yes	EMG	Not reported
Wang et al[27]	2018	Two-point discrimination predicts pain relief after lower limb nerve decompression for painful diabetic neuropathy	China	JPRS	Retrospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Not reported
Liao et al[22]	2018	Mechanical allodynia predicts better outcome of surgical decompression for painful diabetic peripheral neuropathy	China	J Reconst Microsurg	Prospective	Common peroneal, deep peroneal, and tarsal tunnel	Yes	VAS	Not reported
Sarmiento et al[26]	2019	Tibial nerve decompression for the prevention of the diabetic foot: a cost–utility analysis using Markov Model simulations	USA	BMJ Open	Comprehensive cohort simulation model	Tarsal tunnel	N/A	Ulcer or amputation	Not reported
Agarwal and Sharma[1]	2021	Our experience of reinnervation of sole in diabetic sensorimotor polyneuropathy: a chance to change the natural history of disease	India	J Clin Orthop Trauma	Prospective	Tarsal tunnel, SN nerve transfer	Yes	Vibration perception threshold	Delayed wound healing (n = 6)

Ann Plast Surg, Annals of Plastic Surgery; An Surg, Annals of Surgery; EMG, electromyography; JAPMA, Journal of American Podiatric Medical Association; J Clin Orthop Trauma, Journal of Clinical Orthopedics and Trauma; JFAS, Journal of Foot and Ankle Surgery; JNLS, Journal of Neurological Surgery; JPRS, Journal of Plastic and Reconstructive Surgery; J Reconst Microsurg, Journal of Reconstructive Microsurgery; SN, saphenous nerve.

Table 3. Demographics of the Randomized Controlled Trials Included in This Review

Authors	No. Patients	Follow-up	Mean Age ± SD (Y)	Gender (M:F)
Zhang et al[9]	Cases: 560 controls: 40	18 mo	58 ± 11.32	260 M:F 300
van Maurik et al[10]	Cases: 38 controls: 38 (contralateral limb)	12 mo	62.7 ± 10.2	22 M:F 16
van Maurik et al[11]	Cases: 40 controls: 40 (contralateral limb)	12 mo	61.2 ± 11	26 M:F 26
van Maurik et al[12]	Cases: 38 controls: 38 (contralateral limb)	12 mo	61.7 ± 10.2	26 M:F 26
Best et al[13]	Cases: 12 controls: 10	12 mo	64 ± 6.4	6 M:F 6

Table 4. Demographics of the Observational Studies Included in this Review

Authors	No. Patients	Mean Follow-up	Mean Age (Y)	Gender (M:F)
Wieman and Patel[14]	26	13 mo	59.6	11 M:F 15
Wood and Wood[4]	33	3 mo	Not reported	Not reported
Aszmann et al[18]	50	4 y	Not reported	Not reported
Rader[16]	39	15 mo	Range (38-83)	Not reported
Valdivia et al[15]	100	12 mo	63.1	56 M:F 44
Siemionow et al[17]	32	6 mo	49.5	10 M:F 22
Karagoz et al[23]	24	8 mo	48	8 M:F 16
Dellon et al[24]	628	12 mo	Not reported	Not reported
Dellon et al[25]	628	4 y	Not reported	Not reported
Nickerson and Rader[19]	65	3 y	74.5	Not reported
Liao et al[20]	306	4 y	59	108 M:F 198
Anderson et al[29]	40	12 mo	64.8	22 M:F 18
Wang et al[27]	34	12 mo	56.4	19 M:F 15
Liao et al[22]	148	2 y	58.5	57 M:F 91
Sarmiento et al[26]	1677 (simulation model)	5 y	66	Not reported
Agarwal and Sharma[1]	32	6 mo	35.6	18 M:F 14
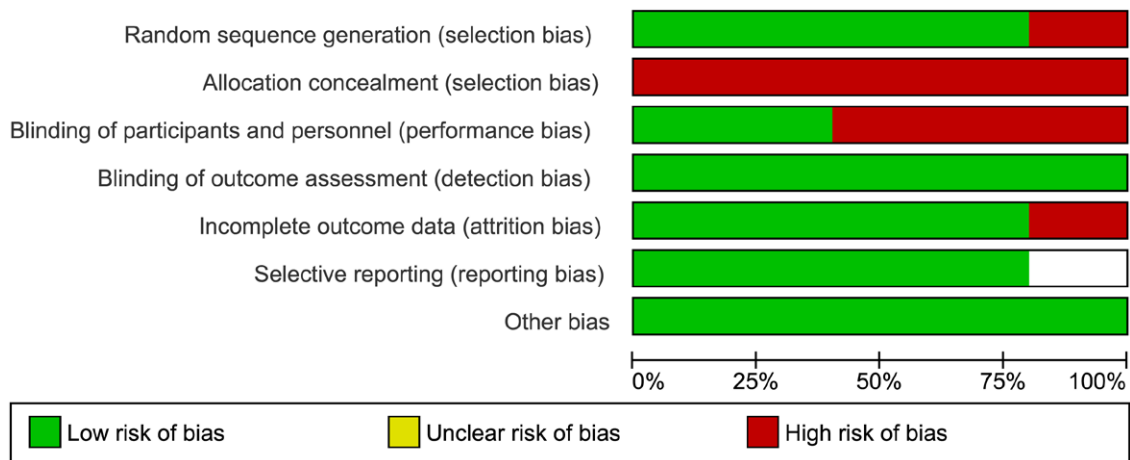
Fig. 2. Risk of bias graph: authors' judgments of included randomized controlled trials using the Cochrane risk-of-bias tool.

respectively. Similarly, the RRs of ulcer development and amputation varied from 0.08 (95% CI, 0.01–0.51) to 0.19 (95% CI, 0.13–0.28) and 0.01 (95% CI, 0.00–0.06) to 0.04 (95% CI, 0.02–0.08), respectively (Table 5).

Subgroup Analysis

A subgroup analysis was performed for the VAS, ulcer development, and amputation outcomes in the observational studies. The 2PD outcome was excluded due to the limited number of articles. The mean difference or RR differed following the study period and number of participants. The mean difference did not differ significantly for VAS outcomes, depending on the study period or number of patients ($P > 0.05$). However, both the study period and number of patients constituted a source of heterogeneity in ulcer development outcomes ($P < 0.05$). Similarly, when the study period was adopted as a moderator in amputation outcomes, the RR differed significantly between the studies ($P < 0.05$). The RR of amputation exhibited a higher trend in studies performed before 2010 than in those performed after 2010 (RR, 0.03 and 0.01, respectively; Table 6). Releasing the tarsal tunnel region tended to be the most effective procedure among the different combinations of lower limb nerve decompressions in terms of type of intervention (Tables 7, 8).
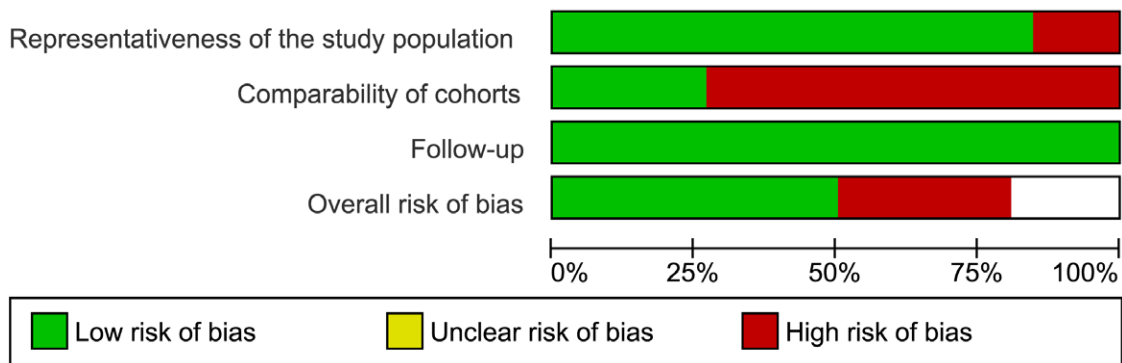
Fig. 3. Risk of bias graph: authors' judgments of included observational studies using the NOS.
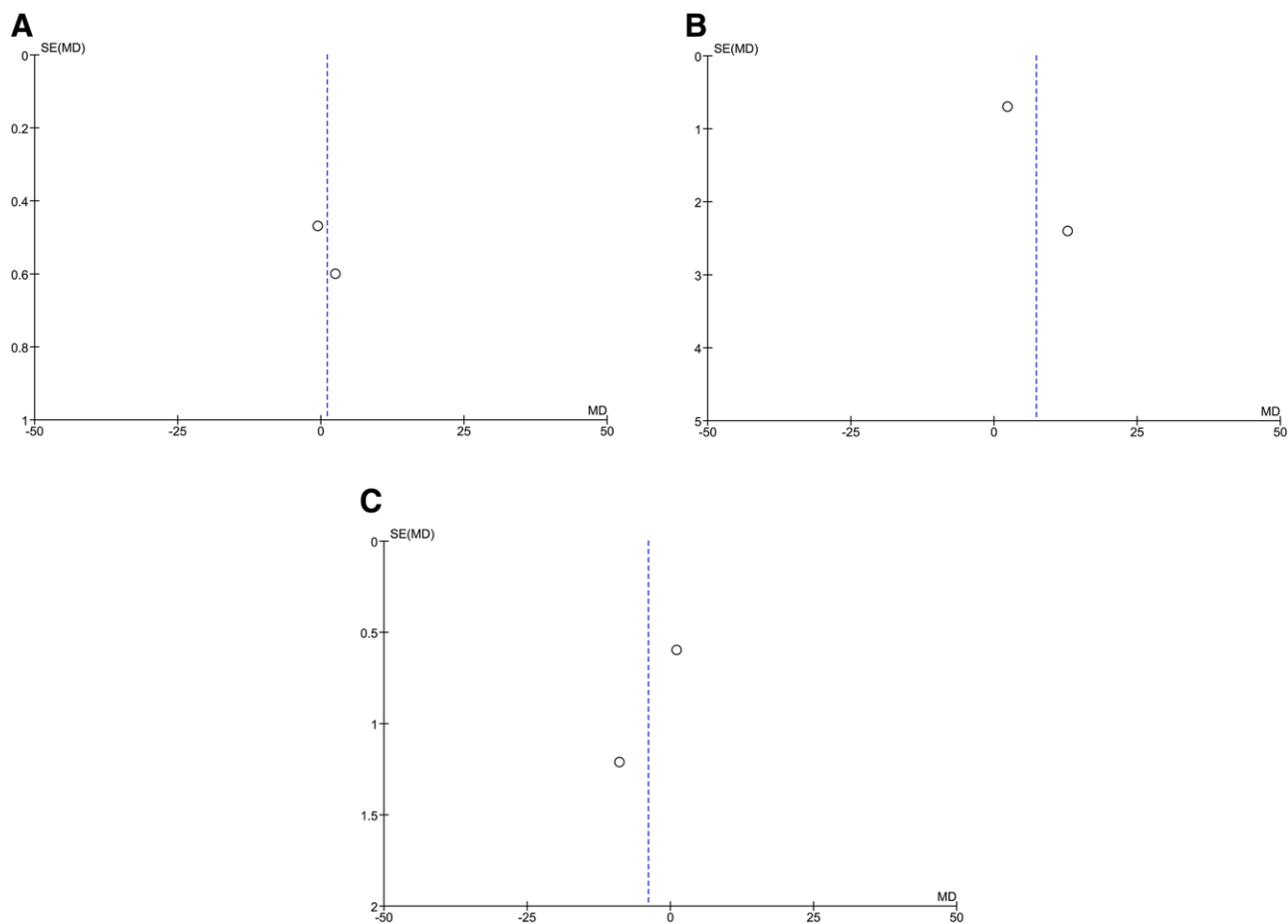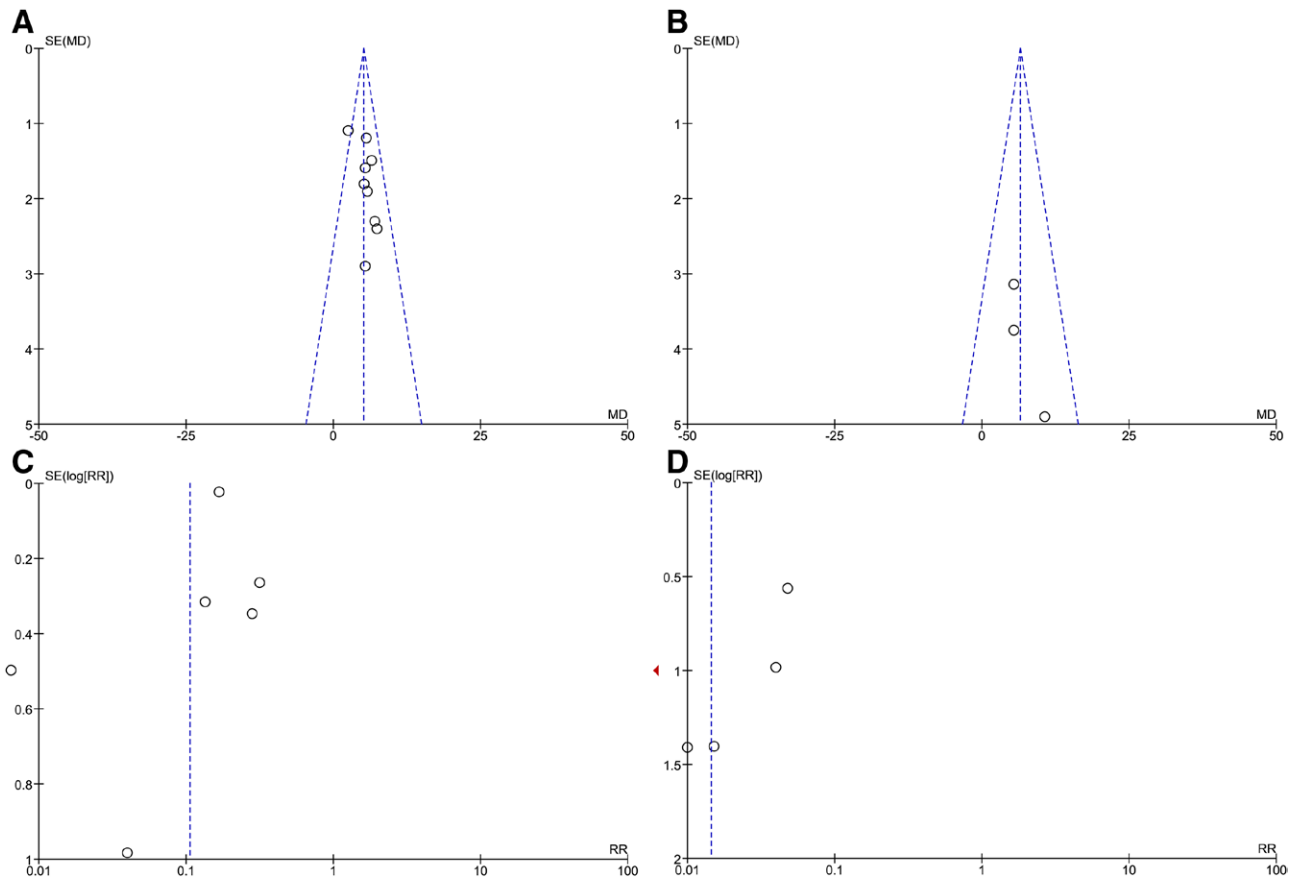

Fig. 4. Funnel plots demonstrating no proof of publication bias in RCTs for the analyzed outcomes. A, VAS. B, 2PD. C, NCV.

DISCUSSION

This study is a detailed systematic review and meta-analysis that specifically examines lower extremity peripheral nerve decompression in DPN. Although Tu et al[30] previously published a systematic review of DPN, most of the articles included in their study focused on carpal tunnel release. With regard to the lower extremity, their analysis was limited to four observational studies, with no reporting of the late sequelae of DPN. Dellon[5] reported a meta-analysis focused on decompressing the tibial nerve

branches at the ankle with 80% improvement in VAS.[31] A meta-analysis by Baltodano et al[32] including 875 diabetic patients was published in 2013. Their study showed a significant improvement in VAS (91%) and sensibility (69%). Additionally, the incidence of postoperative ulceration and amputation was significantly reduced. Our pooled analysis included a total of 21 articles, five RCTs, and 16 observational studies, with 2169 patients. The meta-analysis of observational studies showed that VAS and 2PD outcomes significantly improved after peripheral nerve

Fig. 5. Funnel plots: demonstrating no proof of publication bias in observational studies for the analyzed outcomes. A, VAS. B, 2PD. C, Ulcer development. D, Amputation.

decompression ($P < 0.00001$ and $P = 0.003$, respectively). Moreover, we detected a significantly low RR of both ulcer development and the need for lower limb amputation ($P < 0.05$). A low number of complications associated with peripheral nerve decompression in DPN were observed (Tables 1, 2).

Peripheral neuropathies have been described in patients with primary (types 1 and 2) and secondary diabetes. This suggests a common etiology based on chronic hyperglycemia, leading to progressive nerve fiber loss. This is the most common of all the late complications of diabetes and creates much suffering among diabetic patients. The late sequelae of peripheral neuropathy include foot ulceration, Charcot neuroarthropathy, and amputation.[33] Patients with DPN require reassurance, education, and periodic follow-up. With improved glycemic control, paresthesia and dysesthesia may diminish over time. On the other hand, compared to well-controlled diabetes, poorly treated diabetes has higher morbidity and complication rates associated with DPN. Complete relief from neuropathy symptoms is rare with the currently available treatment modalities. Therefore, most patients with DPN experience a poor quality of life. Unfortunately, less than a third of patients achieve adequate pain control, and ulcers or amputations are prevalent.[34]

Peripheral nerve decompression in patients with DPN was explored as a treatment option in multiple studies.

Tu et al[30] reported significant improvement in symptom severity and the functional status of the upper extremities following carpal tunnel release in patients with DPN. In addition, electrodiagnostic studies of the median nerve showed significant improvements in distal motor latency and sensory conduction velocity. The meta-analysis by Tu et al[30] included only four observational studies exploring lower extremity peripheral nerve decompression. Their study reported clinically and statistically significant improvements in VAS scores and 2PD, which supports our findings. However, the clinical application of this surgical intervention is still low. This could be due to the lack of convincing evidence for performing surgery in a metabolic disease setting.

Improvements in DPN symptoms following peripheral nerve decompression were investigated in multiple studies. Theories related to nerve swelling and edema are often offered as explanations for improvement. The hydrophilic property of sorbitol can lead to increased water content within the nerves of diabetic patients. Additionally, the inflammatory reaction to oxygen-derived free radicals secondary to hyperglycemia and dyslipidemia results in further edema formation.[35,36] Increased nerve volume leads to a high possibility of compression while passing through an anatomical fibro-osseous tunnel. This can produce nerve ischemia, axonal loss, and demyelination injury.
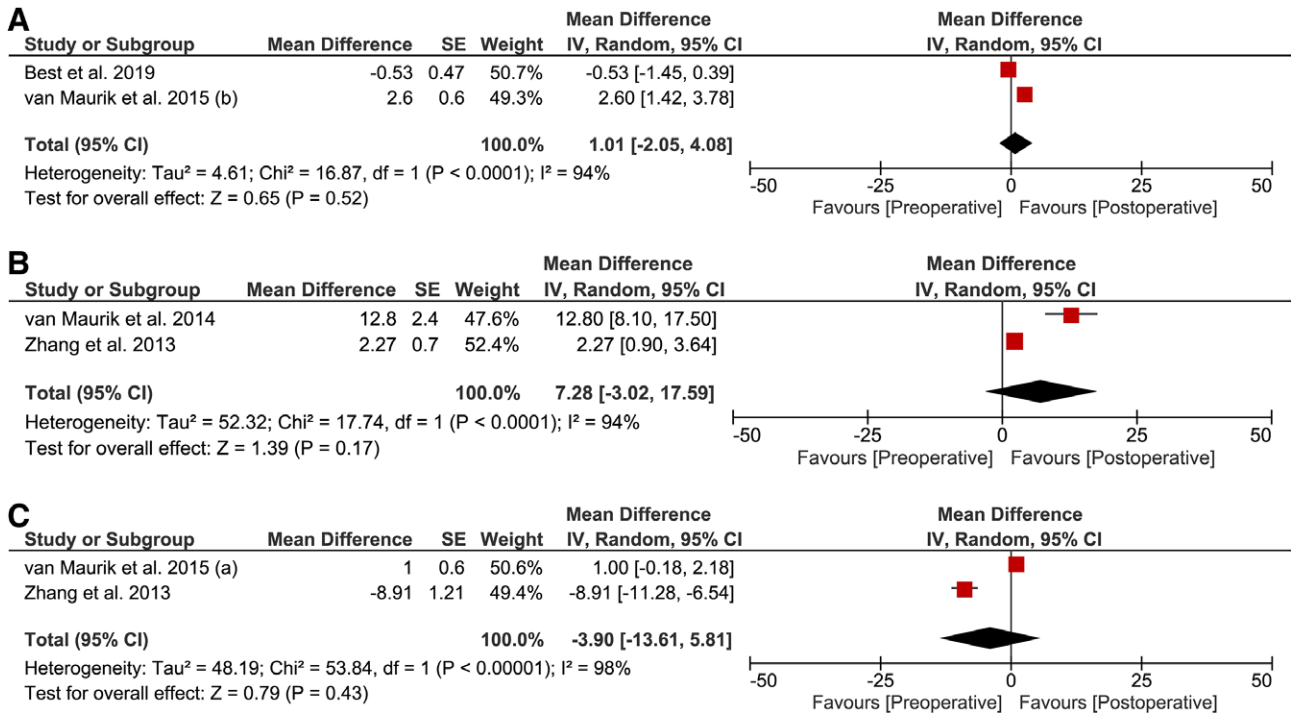
Fig. 6. Forest plots of pooled analysis of outcomes in RCTs. A, VAS. B, 2PD. C, NCV.
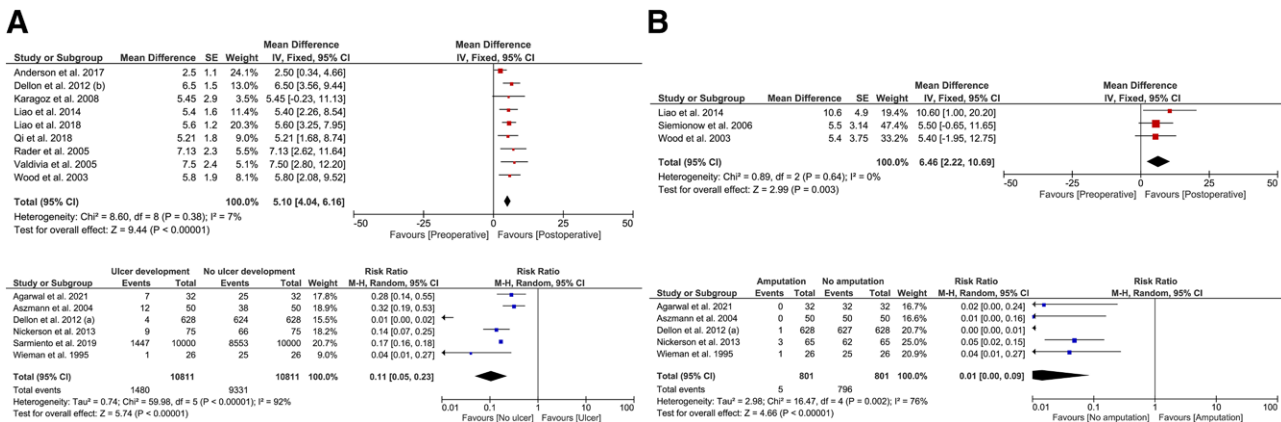

Fig. 7. Forest plots of pooled analysis of outcomes in observational studies. A, VAS. B, 2PD. C, Ulcer development. D, Amputation.

Despite the observed clinical improvement in DPN symptoms following peripheral nerve decompression, clearly, no changes are anticipated to the underlying metabolic neuropathy.[37] Similarly, small favorable changes that might be observed on electrodiagnostic testing are unlikely to be due to effects on the metabolic neuropathy, but rather related to the decompression itself.

In 1992, Dellon[5] reported 85% improvement of DPN symptoms following tibial nerve decompression in the ankle. Aszmann et al[3] observed that peripheral nerve decompression in patients with diabetes improves sensibility and sensory impairment, and restores protective sensation.[38] Peripheral nerve decompression also enhances microcirculation in the feet,[39] improves the plantar sensations, and prevents ulcers and their associated complications.[40] Nerve decompression had a positive effect on the hemodynamic and morphological parameters of arteries as they pass through anatomical tunnels. Furthermore, nerve decompression improved the neurological function of entrapped nerves in addition to pedal sensibility and balance.[41,42] Nerve decompression was found to be an effective and safe treatment for intractable painful DPN with superimposed nerve compression.[43] Anderson et al[29] observed significant improvement in intraoperative electromyography (EMG) immediately following nerve decompression. In addition, two studies from the same group, Zhong et al[44] and the RCT by Zhang et al,[9] reported that DPN patients' NCV improved significantly 18 months after nerve decompression compared with the baseline. Their study suggested that early diagnosis and subsequent peripheral nerve decompression were associated with a favorable clinical outcome.

Table 5. Leave-one-out Sensitivity Analysis of Mean Difference of Analyzed Outcomes among Observational Studies

Outcome	Study Excluded	Mean Difference or RR (95% CI)	P
VAS	Anderson et al[29]	MD, 5.93 (4.71–7.15)	<0.00001
	Dellon et al[25]	MD, 4.89 (3.76–6.03)	<0.00001
	Karagoz et al[23]	MD, 5.09 (4.01–6.17)	<0.00001
	Liao et al[20]	MD, 5.06 (3.94–6.19)	<0.00001
	Liao et al[22]	MD, 4.98 (3.79–6.16)	<0.00001
	Wang et al[27]	MD, 5.09 (3.98–6.20)	<0.00001
	Rader[16]	MD, 4.98 (3.89–6.07)	<0.00001
	Valdivia et al[15]	MD, 4.97 (3.89–6.06)	<0.00001
	Wood and Wood[4]	MD, 5.04 (3.94–6.15)	<0.00001
2PD	Liao et al[20]	MD, 5.46 (0.74–10.18)	0.02
	Siemionow et al[17]	MD, 7.32 (1.48–13.16)	0.01
	Wood and Wood[4]	MD, 6.98 (1.80–12.17)	0.008
Ulcer development	Agarwal and Sharma[1]	RR, 0.08 (0.03–0.21)	<0.00001
	Aszmann et al[18]	RR, 0.08 (0.03–0.21)	<0.00001
	Dellon et al[24]	RR, 0.19 (0.13–0.28)	<0.00001
	Nickerson and Rader[19]	RR, 0.10 (0.04–0.25)	<0.00001
	Sarmiento et al[26]	RR, 0.08 (0.01–0.51)	<0.00001
	Wieman and Patel[14]	RR, 0.12 (0.05–0.26)	<0.00001
Amputation	Agarwal and Sharma[1]	RR, 0.01 (0.00–0.12)	0.0001
	Aszmann et al[18]	RR, 0.02 (0.00–0.13)	0.0002
	Dellon et al[24]	RR, 0.04 (0.02–0.08)	<0.00001
	Nickerson and Rader[19]	RR, 0.01 (0.00–0.06)	<0.00001
	Wieman and Patel[14]	RR, 0.01 (0.00–0.11)	<0.00001

Table 6. Subgroup Analysis for the Mean Difference and RR of Analyzed Outcomes among Observational Studies

Outcomes	Subgroups	No. Studies	Mean Difference or RR (95% CI)	P	Heterogeneity χ2	I² (%)	P
VAS			Study period				
	Before 2010	4	MD, 6.47 (4.22–8.72)	<0.00001	0.51	0	0.92
	After 2010	5	MD, 4.71 (3.51–5.91)	<0.00001	6.27	36	0.18
			No. patients				
	<100	5	MD, 4.23 (2.74–5.72)	<0.00001	5.22	23	0.27
	>100	4	MD, 5.98 (4.48–7.48)	<0.00001	0.75	0	0.86
Ulcer development			Study period				
	Before 2010	2	RR, 0.13 (0.01–1.30)	0.08	5.39	81	0.02
	After 2010	4	RR, 0.09 (0.03–0.26)	<0.00001	51.60	94	<0.00001
			No. patients				
	<100	4	RR, 0.20 (0.10–0.37)	<0.00001	8.68	65	0.03
	>100	2	RR, 0.03 (0.00–1.04)	0.05	48.89	98	<0.00001
Amputation			Study period				
	Before 2010	2	RR, 0.03 (0.01–0.12)	<0.00001	0.75	0	0.39
	After 2010	3	RR, 0.01 (0.00–0.22)	0.003	15.45	87	0.0004
			No. patients				
	<100	4	RR, 0.04 (0.02–0.08)	0.64	1.69	0	0.64
	>100	1	ND	ND	ND	ND	ND

ND, non-detectable.

Table 7. Subgroup Analysis of the Type of Intervention in Observational Studies

Outcomes	Subgroups	No. Studies	Mean Difference or RR (95% CI)	P	Heterogeneity χ2	I² (%)	P
VAS	Intervention						
	Common peroneal, deep peroneal, and tarsal tunnel	7	MD, 5.81 (4.48–7.15)	<0.00001	1.05	0	0.98
	Common peroneal nerve decompression	1	MD, 2.50 (0.34–4.66)	0.02	ND	ND	ND
	Tarsal tunnel	1	MD, 6.50 (3.56–9.44)	<0.00001	ND	ND	ND
Ulcer development	Intervention						
	Tarsal tunnel	3	RR, 0.04 (0.00–0.48)	0.01	51.25	96	<0.00001
	Common peroneal, deep peroneal, and tarsal tunnel	1	RR, 0.32 (0.19–0.53)	<0.00001	ND	ND	ND
	Tarsal tunnel, SN nerve transfer	1	RR, 0.28 (0.14–0.55)	0.0002	ND	ND	ND
	Common peroneal and tarsal tunnel	1	RR, 0.14 (0.07–0.25)	<0.00001	ND	ND	ND
Amputation	Intervention						
	Tarsal tunnel	2	RR, 0.01 (0.00–0.33)	0.01	7.28	86	0.007
	Common peroneal, deep peroneal, and tarsal tunnel	1	RR, 0.01 (0.00–0.16)	0.001	ND	ND	ND
	Common peroneal and tarsal tunnel	1	RR, 0.05 (0.02–0.15)	<0.00001	ND	ND	ND
	Tarsal tunnel and SN nerve transfer	1	RR, 0.02 (0.00–0.24)	0.003	ND	ND	ND

ND, non-detectable; SN, saphenous nerve.

Table 8. Procedure(s) Associated with the Most Significant Changes in Outcomes among Observational Studies

Outcome	Procedure(s)
Lowest risk for ulcer development	1. Decompression of the tarsal tunnel region* 2. Combined common peroneal and tarsal tunnel region decompression*
Lowest risk for amputation	1. Combined common peroneal, deep peroneal, and tarsal tunnel region decompression* 2. Decompression of the tarsal tunnel region
Most significant reduction in the VAS	1. Decompression of the tarsal tunnel region* 2. Combined common peroneal, deep peroneal, and tarsal tunnel region decompression*

*Decompression of the tarsal tunnel region includes releasing the tibial nerve and its branches in all four tunnels around the (1) ankle tarsal tunnel, (2) medial plantar tunnel, (3) lateral plantar tunnel, and (4) calcaneal tunnel.

The findings from this meta-analysis highlight the efficacy of peripheral nerve decompression among DPN patients. This was demonstrated by the significant improvement in VAS and 2PD after operation in observational studies. Further analysis of observational studies showed a significant low RR of ulcer development and amputation following intervention. On the other hand, pooled data meta-analysis of VAS, 2PD, and NCV outcomes were not significantly improved after operation in the RCT studies. This could be attributed to high heterogeneity and a limited number of RCTs included in the analysis of each outcome measure. Thus, large-scale clinical studies are needed to provide stronger evidence that would support offering this intervention to patients with DPN.

The subgroup analyses detected a tendency towards decompression of the tarsal tunnel region as the most effective procedure in reducing symptoms and complications of DPN. This is likely related to the importance of plantar sensation in preventing repeated trauma to the foot. The Dellon[5] approach was followed in multiple studies for decompressing the tibial nerve and its branches in the tarsal tunnel region. This included the surgical release of four tunnels: (1) tarsal tunnel, (2) medial plantar tunnel, (3) lateral plantar tunnel, and (4) calcaneal tunnel.[31] The Hoffmann-Tinel sign was utilized as an indication for surgery in most of the studies included in this review (Tables 1, 2). A positive test was previously shown to have a 92% positive predictive value for a favorable outcome following the decompression of tarsal tunnels in DPN.[45]

Limitations

Despite the low heterogeneity shown in the outcomes of the observational studies included in our meta-analysis, RCT studies had high heterogeneity for VAS, 2PD, and NCV. This could be attributed to the limited number of articles included in the analysis of each outcome. Other RCTs were excluded from the analysis due to variability in surgical intervention or reported outcome measures. However, to control for the previously stated limitations, sensitivity analyses were conducted. The results indicated the strong reliability of the meta-analysis and the absence of publication bias for the outcomes analyzed.

CONCLUSIONS

The meta-analysis of observational studies in this report highlights the efficacy of lower extremity peripheral nerve decompression in reducing symptoms, ulcerations, and amputations related to DPN. Releasing the tibial nerve in the tarsal tunnel region was the most effective observed procedure. Nevertheless, high-quality RCTs are required to support the utility of this intervention in this patient population.

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