R E V I E W

Compression Therapy for Prevention of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Zhanhai Wan [ID][1], Jiajie Huang[2], Xiumei Wang [ID][1], Peng Li [ID][1]

[1]Department of Anesthesiology and Operating Theater, The First Hospital of LanZhou University, Lanzhou, Gansu, People's Republic of China; [2]School of Nursing, Gansu University of Chinese Medicine, Lanzhou, Gansu, People's Republic of China

Correspondence: Peng Li, Email Leepeng19771125@163.com

Background: Chemotherapy-induced peripheral neuropathy (CIPN) significantly impairs the quality of life of patients undergoing chemotherapy and diminishes their adherence to the treatment regimen. Existing studies suggest that compression therapy may prevent the onset of CIPN, yet the specific efficacy remains to be conclusively determined.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing compression therapy with inactive comparators in patients scheduled for chemotherapy. Evidence certainty was evaluated using the GRADE approach.

Results: Analysis of four trials (442 patients) revealed that compression therapy reduced CIPN incidence (RR = 0.50, 95% CI: 0.33–0.76; absolute effect = −265, 95% CI: −355 to −127 per 1000) and depression (SMD = −0.83, 95% CI: −1.21 to −0.45) with moderate evidence and high adherence. No significant differences emerged in anxiety, sleep quality, or pain.

Conclusion: Moderate- to low-certainty evidence supports compression therapy's effectiveness in preventing CIPN and alleviating depression while showing no substantial impact on other outcomes.

Limitation: Evidence quality and quantity suggest potential bias, warranting additional RCTs to strengthen the evidence base.

Keywords: compression therapy, CIPN, RCT

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) affects 30–40% of patients receiving neurotoxic chemotherapy.[1,2] It often presents as a pure sensory neuropathy, with symptoms of numbness, tingling, and pain in the hands and feet that can persist for years after treatment and can impact quality of life, limit daily functioning and lead to early termination of treatment.[3,4] Despite numerous studies on the prevention of CIPN, effective management of this condition remains a challenge.[5–7]

The current guidelines by the American Society of Clinical Oncology (ASCO) for the management of moderate CIPN advocate the use of duloxetine as a therapeutic intervention.[8] However, duloxetine is prone to causing adverse reactions such as drowsiness and thirst, and has poor tolerance. To make treatment measures applicable to all patients and to minimize the side effects and discomfort of intervention measures, some researchers have begun to consider using acupuncture, exercise, compression therapy, cryotherapy, and other physical therapies for the treatment and prevention of CIPN.[9–11] Among them, compression therapy has gradually attracted attention due to its simple operation and high compliance. There is evidence that compression therapy using surgical gloves can decrease the incidence of CIPN;[12] several recent randomized controlled trials (RCTs) have investigated the associations between Compression therapy and CIPN. To our knowledge, there are no reviews

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about the effects of Compression therapy on CIPN prevention. Therefore, our aim is to conduct a comprehensive assessment of the effectiveness of compression therapy in preventing CIPN.

Methods

We registered the protocol of this systematic review and meta-analysis in the PROSPERO database (registration number: CRD42024553025). The study methodology and result reporting strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Search Strategy

A comprehensive literature search was performed across multiple databases including PubMed, Embase, Web of Science, CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov, and three Chinese databases (CNKI, Wanfang, and Sinomed). The search covered the period from each database's inception through June 2024. We used the following combination of search terms: (compression therapy) AND (Peripheral Nervous System Diseases). For the detailed search strategy see Supplementary Table S1. The researchers tracked the reference lists of the identified studies and existing systematic reviews to identify eligible studies.

Selection Criteria

We included RCTs that allocated adult cancer patients (>18 years of age) planned to be treated with chemotherapy, in whom the compression therapy compared with any inactive comparator (including usual care or sham intervention) is eligible for inclusion, and the outcome used was incidence of CIPN. We included randomized clinical trials (RCTs) of any design. Abstracts without any usable data were excluded.

Study Selection

The initial screening of titles and abstracts was conducted using Rayyan, an online literature management platform.[14] Articles that passed initial screening underwent detailed full-text assessment, with reasons for exclusion documented using a standardized eligibility form. Paris of reviewers independently and in duplicate completed the study selection process and then engaged in a thorough discussion to resolve any discrepancies.

Data Extraction

Data extraction was performed independently by two reviewers utilizing a standardized collection form. Key information extracted from each eligible study encompassed the first author's surname, publication year, study location (country), follow-up duration, study type (blinded or open-label RCT), participant characteristics (demographics, clinical diagnosis etc.), intervention details (intervention time etc.), comparator type (usual care, sham intervention etc.), and outcome measures (eg, the CTCAE scores). Reviewers engaged in a thorough discussion to resolve any discrepancies. When eligibility criteria could not be fully assessed due to missing information, we will reach out to the corresponding authors for additional details.

Outcomes

We examined the incidence of CIPN as the primary outcome. CIPN was defined individually in every study, because there is currently no gold standard for diagnosis. Most studies used the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) and the Functional Assessment of Cancer Therapy Neurotoxicity (FACT-NTX). Typically, the incidence of CIPN is considered to have occurred when a patient's NCI-CTCAE ≥ 2 score, and FACT-NTX score has decreased $\leq 10\%$ or 5 score. The secondary outcomes were finger adherence, anxiety, depression, sleep quality and pain.

Risk of Bias Assessment

Two independent reviewers assessed the risk of bias in individual trials using the Cochrane risk of bias assessment tool, with any disagreements resolved through discussion.[15] The instrument addressed the following domains: random sequence

generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome, selective reporting and other bias. Each investigator assessed each domain of "low", "some concerns", or "high".

Data Synthesis

We utilized random-effects meta-analyses, which take into account both within-study and between-study variances in the calculation of the error term for the analysis.[16] The random-effects model enhances the clinical applicability of our findings by allowing broader generalization beyond the included studies and populations. We employed various methods to enhance the interpretability of the meta-analysis results. For trials reporting binary outcomes, we calculated the relative risk (RR) to convey relative effectiveness. Additionally, we reported the absolute risk reduction and obtained estimates of baseline risk from observational studies identified through focused literature searches. If such estimates were not available, we derived them from the median baseline risk in the control groups of eligible randomized controlled trials. When the distribution was relatively normal, we analyzed categorical data as continuous data; if not, we collapsed the data into binary variables. When pooling trials that reported continuous endpoints using the same instrument, we calculated the mean difference (MD). When pooling trials that reported continuous endpoints using different instruments, We have calculated Cohen's d, which represents the standardized mean difference (SMD).[17] For studies with sufficient data (≥10 trials), publication bias evaluation would combine visual funnel plot asymmetry assessment with quantitative Egger test analysis.[18] We performed all analyses using RevMan 5.4 and Stata 18.

Subgroup Analyses and Meta-Regression

Statistical heterogeneity was evaluated using the Cochran Q test and I2 statistic. To minimize multiplicity and avoid data fishing, we pre-specified two potential subgroup analyses: (1) risk of bias (low vs high), with a predefined hypothesis of larger effects in high-risk studies, and (2) follow-up duration (<10 vs >10 years), hypothesizing larger effects with longer follow-up. Subgroup analyses would be conducted if at least 2 studies were available per subgroup, using interaction tests to determine between-group differences and the ICEMAN tool to assess subgroup effect credibility.[19] Meta-regression for intervention duration was planned for cases with ≥10 observations, following Cochrane guidelines.[20] However, due to the limited number of included studies, neither subgroup analyses nor meta-regression were performed.

Certainty of Evidence

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, with initial assessment by one reviewer and verification by another.[21] Following the GRADE framework, evidence from RCTs began at high certainty and could be downgraded based on five domains: risk of bias, inconsistency, indirectness, imprecision, or publication bias. We judged as serious inconsistency due to the I^2 value between 75% and 100% indicates or the confidence intervals (CI) overlap to a low extent. Imprecision was rated as serious when CIs crossed the threshold of clinical importance or when sample sizes failed to meet the optimal information size, calculated according to GRADE guidelines on imprecision.

Results

The literature search yielded 1942 records, of which 22 underwent full-text review after initial title and abstract screening. Ultimately, 4 trials (reported in 5 publications) met the inclusion criteria, encompassing a total of 442 participants (Figure 1).[22–26] Details of excluded studies are provided in Table S2.

Study Characteristics

An overview of the study characteristics of these studies is shown in the Table 1. Overall, participants were primarily from China and the United States, with an average age ranging from 50 to 62 years. The sample size of each study ranged from 63 to 186. Two of the trials were sponsored by the government,[22,26] and one was sponsored by institution.[22,26] Three of the trials focused on breast cancer patients,[22,24,26] and one on lung cancer patients.[23] All trials applied pressures within the range of 20–32 mmHg. Adherence was defined differently in each trial and varied from 72.6% to 98.3%. Most of trials utilized conventional treatment as a control, while Accordino's[24] selection employed loose long-sleeved tops and gloves as a control. Three trials opted to assess
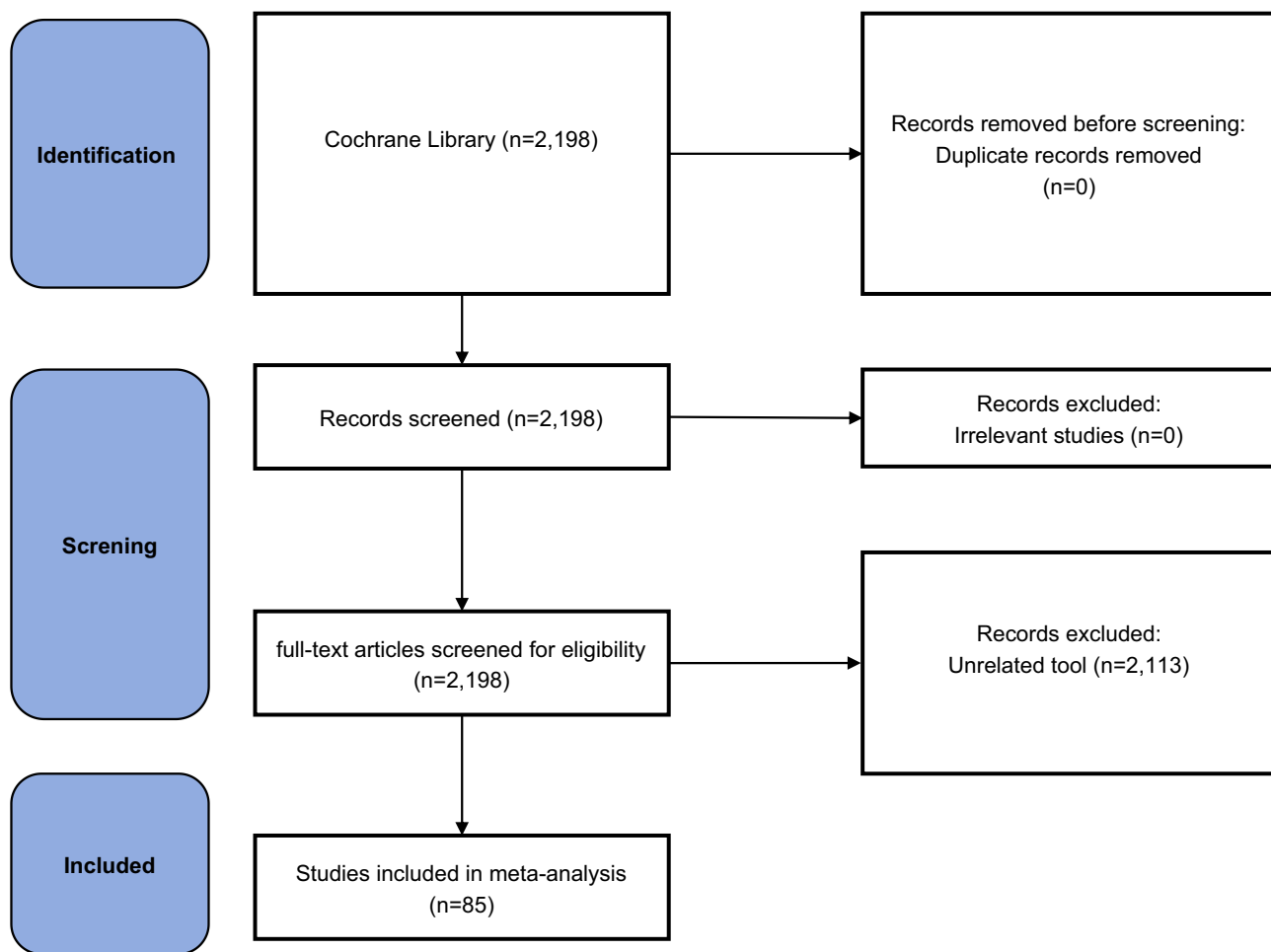
Figure 1 Literature screening flow diagram.

CIPN used the NCI-CTCAE scale, whereas Accordino[24] chose the FACT-NTX scale for CIPN assessment. All trials followed up with patients for a minimum of 12 weeks, with an average follow-up duration of 16.4 weeks (SD 5.7).

Risk of Bias
The risk of bias assessment is summarized in Table 2 and Figure 2. While all included trials demonstrated bias risk in at least two domains, randomization sequence was adequately generated in 2 trials (50%). None of the trials reported proper allocation concealment, and only 1 trial (25%) implemented blinding of patients and researchers. Outcome assessor blinding was absent across all trials. However, none of the trials reported substantial missing outcome data (≥20%).

Outcomes
The GRADE evidence summary, including effect sizes, absolute effects, and quality assessment for each outcome, is presented in Table 3. The results of sensitivity analyses, as shown in Figures S1–S4, demonstrate that the findings are robust. We did not conduct subgroup analyses and meta-regression to explore factors affecting the results, as the overall number of included studies in each outcome <10, and the number of studies in each subgroup <2.

Incidence of CIPN
Pooled analysis of 4 RCTs (442 patients) demonstrated that compression therapy significantly reduced CIPN incidence compared to placebo or usual care (RR = 0.50, 95% CI: 0.33–0.76, moderate, Figure 3). Given a baseline risk of 532 per 1000, this represents an absolute reduction of 265 fewer cases per 1000 patients (95% CI: 355 to 127 fewer).

Table 1 Study Characteristics

Reference	Country	Patients (n)	Age (mean, SD)	Women (n, %)	Type of cancer	Chemotherapy drugs	Compression Technique	Pressure	Duration	Comparison Group	Follow-up Duration (Week)	Mearsure	Funding
Chen 2023[27]	China	186	49.7 (7.4)	62 (100%)	Breast cancer	PTX	Surgical gloves or self-inflating pressure cuff	23~32 mmHg	During chemotherapy and 15 minutes before and after chemotherapy,	Usual care	12	NCI-CTCAE	Government
He 2023[22]	China	123	62 (8.6)	38 (30.9%)	Lung cancer	PTX	Surgical gloves and compression stockings	23~32 mmHg	During chemotherapy and 30 minutes before and after chemotherapy	Usual care	12	NCI-CTCAE	NR
Accordino 2024[23]	USA	63	53 (14.2)	43 (100%)	Breast cancer	PTX	Sigvaris CompreFlex Transition and Sigvaris Secure Arm sleeves Gloves	20–30 mmHg	During chemotherapy and 15 minutes before and after chemotherapy	Placebo with "Loose" Gloves/Socks	24	FACT-NTX	Institution
Guo 2024[24]	China	80	51.54 (10.6)	80 (100%)	Breast cancer	PTX	Surgical gloves and elastic socks	23~32 mmHg	During chemotherapy and 30 minutes before and after chemotherapy	Usual care	18	NCI-CTCAE	Government

Table 2 Risk of Bias Summary

Name, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome	Selective Reporting	Other Bias
Chen 2023[27]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
He 2023[22]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Accordino 2024[23]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Guo 2024[24]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk

Anxiety

two RCTs (116 patients) reported anxiety. Due to the use of different scales (HADS and PROMIS-29) in the included studies, SMD was calculated. Compared with placebo and usual care, compression therapy was not associated with anxiety (SMD = −0.41, 95% CI: −1.89–1.07; very low, Figure 4).

Depression

Two RCTs (116 patients) reported anxiety. Due to the use of different scales (HADS and PROMIS-29) in the included studies, SMD was calculated. Compared with placebo and usual care, compression therapy was associated with depression (SMD = −0.83, 95% CI: −1.21 to −0.45; low, Figure 5).

Figure 2 Risk of bias summary.

Table 3 Evidence for All Included outcomes Summary

Outcome	No. of trials (no. of patients)	Effect size (95% CI)	Risk of bias	Inconsistency, (I^2, %)	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Absolute effect (95% CI)
Incidence of CIPN	4 (442)	RR=0.48 (0.32–0.73)	Serious[a]	Not serious (58)[b]	Not serious	Not serious	Undetected	Moderate	−265 (−355 to −127) per 1000; baseline risk: 532 per 1000
Anxiety	2 (116)	SMD=−0.41 (−1.89–1.07)	Serious[a]	Serious (92)[b]	Not serious	Very serious[c]	Undetected	Very low	NA
Depression	2 (116)	SMD=−0.83 (−1.21–0.45)	Serious[a]	Not serious (0)[b]	Not serious	Serious[d]	Undetected	Low	NA
Sleep quality	2 (116)	SMD=−0.47 (−1.67–0.72)	Serious[a]	Serious (92)[b]	Not serious	Very serious[c]	Undetected	Very low	NA
Pain	1 (36)	MD=−0.50 (−2.69–1.69)	Not serious	Not serious (heterogeneity not applicable)	Not serious	Very serious[c]	Undetected	Low	NA

Notes: [a]judged as serious due to most the lack of concealed allocation and the absence of blinding. [b]An I^2 value between 75% and 100% indicates that heterogeneity may be considerable. [c]Judged as very serious due to the confidence intervals span the threshold and the sample size does not achieve optimal information power. [d]Judged as serious due to the sample size does not achieve optimal information size.
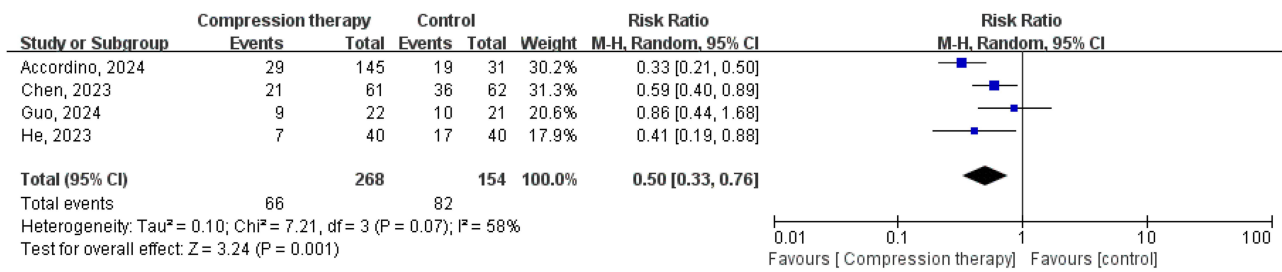
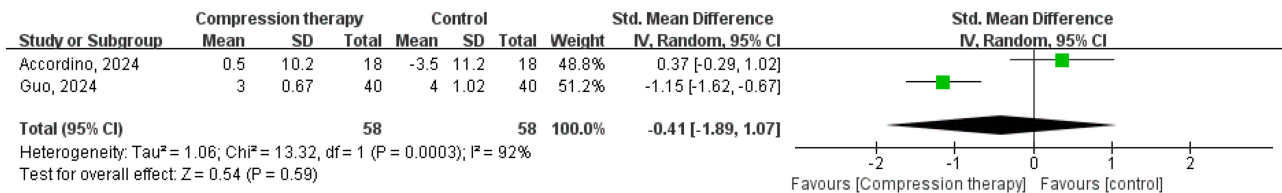**Figure 3** Results of the meta-analysis of the incidence of CIPN.

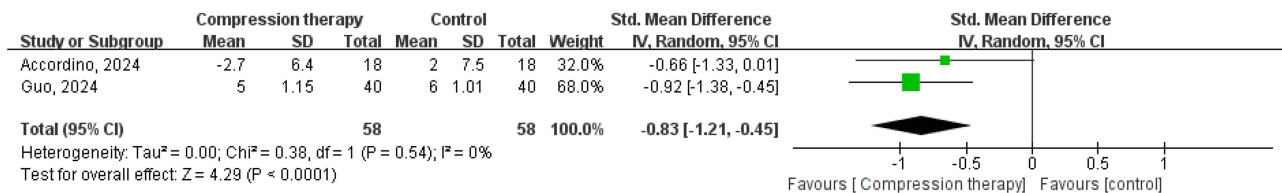**Figure 4** Results of the meta-analysis of anxiety.

Figure 5 Results of the meta-analysis of depression.

Sleep Quality

Two RCTs (116 patients) reported anxiety. Due to the use of different scales (HADS and PROMIS-29) in the included studies, SMD was calculated. Compared with placebo and usual care, compression therapy was not associated with sleep quality (SMD =-0.47, 95% CI: −1.67–0.72; very low, Figure 6).

Pain

One RCTs (36 patients) reported anxiety. Due to only one scales was used in the included studies, MD was calculated. Compared with placebo and usual care, compression therapy was not associated with sleep quality (MD = −0.50, 95% CI: −2.69 to 1.69; low; Figure 7).
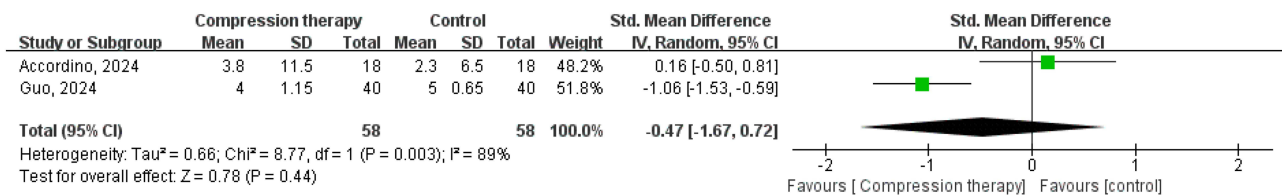

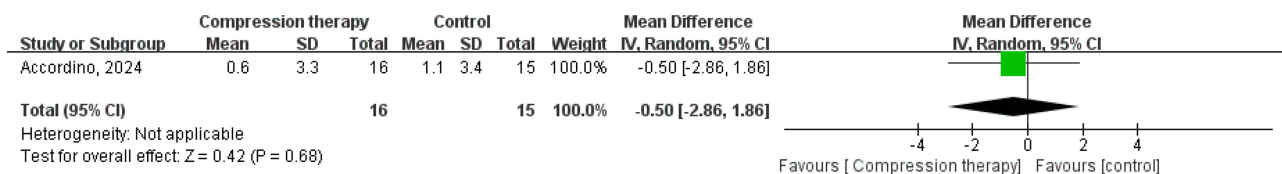**Figure 6** Results of the meta-analysis of sleep quality.

Figure 7 Results of the meta-analysis of pain.

Discussion

Main Findings

This comprehensive systematic review and meta-analysis evaluated the efficacy of compression therapy for CIPN prevention. We found moderate-certainty evidence that compression therapy may result in an absolute reduction of 265 per 1000 patients on incidence of CIPN, with high adherence (72.6% to 98.3%) in the same population. Additionally, low-certainty evidence suggested potential benefits in reducing depression. However, other outcomes showed no significant associations, supported by low to very low certainty evidence. Given the variable evidence quality across outcomes, additional well-designed RCTs are warranted to strengthen the current evidence base.

Comparison with Other Reviews

This is the first systematic review investigating compression therapy on the prevention of CIPN in people with cancer. Although numerous studies have been published on the use of compression therapy in conditions, such as deep vein thrombosis,[28] varicose veins,[29] or lymphedema,[30] there are relatively few studies assessing its role in preventing CIPN in cancer patients. Most current studies on the use of compression therapy for CIPN prevention in cancer populations have utilized self-controlled trial methods[31–33] (one hand of the patient undergoes compression therapy, while the other hand undergoes comparator). The limitation of this research method is that the two hands of the same patient are considered independent, which cannot rule out the influence of the pressure applied to the study side on the control side. Therefore, this review only included randomized controlled trials where both hands underwent compression therapy or control simultaneously. The results from the randomized controlled trials were consistent with most of the self-controlled trials, both supporting the effect of compression therapy on preventing CIPN Additionally, the findings of this review are in line with the evidence from the ASCO guidelines,[8] indicating that compression therapy can prevent CIPN. However, our review includes more trials, a larger patient population, and our methodological approach, including GRADE assessment and presentation of absolute effects, enhances the clinical interpretability of results. These comprehensive analyses provide robust evidence to inform future guideline development.

Potential Interpretations of Findings

Microtubule function inhibition induced by chemotherapeutic agents results in structural and functional neuronal damage, leading to clinically manifested peripheral neuropathy.[34] The severity of neuronal impairment is contingent upon multiple variables, including pharmaceutical agents, cumulative dosage, and therapeutic duration. Compression therapy, through the application of controlled pressure to the extremities, induces vasoconstriction and subsequent reduction in peripheral blood flow, thereby attenuating chemotherapeutic agent exposure to peripheral nerves, diminishing cytotoxicity, and reducing the incidence of chemotherapy-induced peripheral neuropathy (CIPN).[12,32] CIPN has been identified as an independent risk factor for anxiety and depression, with approximately 40% of CIPN patients experiencing psychological distress. The neuropathic pain associated with CIPN demonstrates a significant correlation with adverse psychological manifestations.[35,36] The amelioration of depressive symptoms through compression therapy in CIPN patients is primarily mediated through indirect mechanisms. CIPN-associated neuropathic pain significantly correlates with psychological distress, and its improvement through compression therapy contributes to enhanced emotional well-being.

Strengths and Limitations

Key strengths of this review include rigorous statistical analyses, incorporating both meta-analytic approaches and sensitivity/precision assessments. This systematic review is based on randomized controlled trials and includes a comprehensive search of eight databases. We ensured that at least two researchers independently conducted the screening, data extraction, risk of bias assessment, and evidence quality grading, and resolved any discrepancies appropriately. We followed PRISMA guidelines for systematic reporting, conducted comprehensive bias assessment, and utilized the GRADE framework provided transparent assessment of evidence certainty, enhancing result interpretation, and calculated absolute effects to clearly interpret the findings, aiding evidence users in better understanding the evidence and facilitating the translation of evidence into decision-making.

This systematic review has notable limitations that warrant consideration. (1) The evidence base was characterized by overall low quality, introducing potential bias from residual confounding and selection factors; (2) external validity was constrained by the predominance of female breast cancer patients receiving taxane-based chemotherapy in the study populations; (3) data limitations prevented comprehensive subgroup analyses, including examination of risk of bias and other potentially relevant factors; (4) publication bias could not be formally assessed due to the small number of included studies (n = 4), though its influence cannot be excluded; (5) The impact of compression therapy on anxiety and sleep quality showed sensitivity to analytical approach; while fixed-effects modeling yielded different results, the substantial heterogeneity observed (I2 = 92% and 89%) suggests greater appropriateness of random-effects analysis.

Given CIPN's dose-dependent toxicity profile, subsequent studies should track and report total chemotherapy exposure throughout the intervention phase.[37] Additionally, we also require a greater number of high-quality RCTs that implement blinding methods to consolidate the findings of the research and further explore the impact of the placebo effect, as we cannot ascertain whether the heterogeneity observed between studies is related to the placebo effect.

Conclusions

Moderate certainty supports that compression therapy can significantly reduce the incidence of CIPN and has high adherence. Low certainty evidence supports that compression therapy can alleviate depressive symptoms in chemotherapy patients, and no significant association was found between compression therapy and other related outcomes, such as anxiety, sleep quality, and pain. The predominantly low to very low certainty of evidence suggests caution in interpreting current findings, highlighting the need for large-scale, methodologically rigorous randomized controlled trials.

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Disclosure

The authors declare that they have no competing interests.

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