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RESEARCH

Efficacy of cryotherapy in the prevention of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis

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Abstract

Purpose The study investigates cryotherapy's efficacy in mitigating Chemotherapy-induced peripheral neuropathy (CIPN), an adverse effect of chemotherapy that often leads to dosage reduction or treatment discontinuation.

Method The study was registered with PROSPERO (CRD42023428936). A literature search was conducted using the PubMed, Embase, and Cochrane Library databases. Randomized and nonrandomized controlled trials that investigated the effects of cryotherapy on CIPN were included for systematic review and meta-analysis. The primary outcome for prevention was the incidence of CIPN.

Results We identified 17 trials involving 2,851 patients. In total, 11 trials compared the incidence of CIPN between cryotherapy and control groups. Significant differences in the incidence of CIPN at the midpoint and end of chemotherapy were observed, with risk ratios (RRs) of 0.23 (95% confidence interval [CI] = 0.13 to 0.43) and 0.54 (95% CI = 0.33 to 0.88), respectively. Cryotherapy also significantly reduced the incidence of sensory CIPN, with an RR of 0.67 (95% CI = 0.49 to 0.92). Additionally, cryotherapy demonstrated a significant reduction in the incidence of CIPN in patients with gynecological cancers (RR = 0.24, 95% CI = 0.14 to 0.41). Significantly favorable global quality of life scores following chemotherapy (standardized mean difference = 1.43; 95% CI = 0.50 to 2.36) and relieved neuropathic symptoms were found with cryotherapy.

Conclusions Cryotherapy demonstrates a pronounced preventive effect against the development of CIPN, providing substantial symptomatic relief and quality of life improvements for patients undergoing chemotherapy. The administration of cryotherapy through the use of frozen gloves and socks, or continuous-flow cooling systems, optimally initiated 15 min prior to and concluded 15 min following chemotherapy, is recommended for achieving maximum therapeutic efficacy.

Keywords Chemotherapy-induced peripheral neuropathy · Cryotherapy · Taxanes · Oxaliplatin

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and debilitating side effect of many anticancer drugs, affecting sensory, motor, and autonomic fibers [1]. Agents notably associated with CIPN include taxanes (e.g., paclitaxel, docetaxel), platinum-based compounds (e.g., cisplatin, oxaliplatin), alkylating agents, and Vinca alkaloids [2, 3]. The prevalence of CIPN is appoximately 68.1% at 1 month and 60.0% at 3 months after chemotherapy, siginificantly impairing patients' quality of life (QoL) and often leading to dose reductions thatdeviate from optimal cancer treatment [3, 4]. CIPN symptoms can be acute, with 89% of patients experiencing sensitivity to cold after the first chemotherapy cycle, or chronic, manifesting as numbness, tingling, allodynia, and neuropathic

pain in 13% to 70% of cases [5, 6]. These symptoms hinder daily activities and diminish overall QoL [7, 8].

Despite advancements in understanding the mechanism of CIPN, an effective treatment remains elusive [1, 9, 10]. Physical therapy, exercise, and acupuncture are frequently discussed but lack sufficient evidence for efficacy and not included in the 2020 guidelines by the American Society of Clinical Oncology [11, 12]. Currently, duloxetine is the only agent recommended for painful CIPN, but its benefits are modest [12].

Cryotherapy, involving regional cooling methods such as frozen gloves and socks, has shown promise in reducing sensory and motor neuropathy and preventing dose reduction [13, 14]. It also alleviates other chemotherapy-induced symptoms like oral mucositis, onycholysis, and alopecia by decreasing perfusion and protecting extremities [15–17]. A meta-analysis published in 2021 suggested cryotherapy is likely to prevent taxane-induced peripheral neuropathy (TIPN), but it did not include the latest clinical trials or other chemotherapy regimens [18]. Given the recent studies and minimal side effects of cryotherapy, we conducted a systematic review and meta-analysis to evaluate the efficacy of cryotherapy in the prevention of CIPN in patients receiving chemotherapeutics.

Materials and methods

The meta-analysis was performed in accordance with the PRISMA guidelines [19]. Our review protocol was registered with PROSPERO (CRD42023428936).

Selection criteria

This study investigated whether cryotherapy was effective in preventing CIPN. Studies applying any kind of physical cooling device to patients' extremities during chemotherapy were included in the analysis. A control group consisted of individuals who did not receive cryotherapy or the control limb contralateral to the intervention limb. Conference abstracts and reviews were excluded. Randomized and nonrandomized trials that involved participants with cancer, that specified the type of cancer and chemotherapy regimen, and that contained objective or subjective assessments were included. Trials that included participants who had peripheral neuropathy developed from diseases other than chemotherapy at baseline, involved intervention subsequent to chemotherapy treatment, or compared cryotherapy with other interventions (such as cryocompression) were excluded.

Search strategy and study selection

Studies were identified by performing computerized searches of the following databases: PubMed, EMBASE, and the Cochrane central register of controlled trials. The following terms were used for MeSH and free-text searches: "(cryotherapy OR hypothermia OR frozen OR cold) AND (neuropathy OR nerve pain) AND (chemo OR cancer OR taxane OR platinum OR vinca alkaloid OR immunomodulatory antiangiogenic agent OR proteasome inhibitor)". Detailed searching strategies are provided in supplementary. The "related articles" function in PubMed was used to broaden the search, and all abstracts, studies, and citations that were retrieved were then carefully reviewed. To identify additional studies, we searched the reference sections of relevant papers and contacted established experts in the field. No language restrictions were applied. The last search was performed in March 2024.

Data extraction

Two independent reviewers (HYT and LYL) extracted trial details pertaining to participants, inclusion and exclusion criteria, types of cancers and chemotherapeutics, cooling strategies, neuropathy parameters, dose reduction, tolerability parameters, quality of life, and adverse events. The individually recorded decisions of the two reviewers were compared, and any disagreements were resolved by a third reviewer (TWH).

Methodological quality appraisal

The first two reviewers (HYT and LYL) independently employed the Cochrane Risk of Bias 2.0 tool to appraise the methodological quality of each randomized controlled trial (RCT) and reported on the following aspects: the randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results [20]. The Risk of Bias in Nonrandomized Studies of Interventions tool was used for the appraisal of nonrandomized controlled trials (NRCTs) in terms of their preintervention, intraintervention, postintervention, and overall biases [21]. Different decisions of two reviewers were compared and resolved by a third reviewer (TWH).

Outcome assessments

The efficacy of cryotherapy was evaluated based on the incidence of CIPN, dose reduction rate due to CIPN, QoL following chemotherapy and neuropathic symptoms. Several but not all studies distinguished between sensory and motor CIPN. Therefore, this study separately analyzed

the incidences of sensory and motor CIPN at the end of chemotherapy and also analyzed the incidence of unspecified CIPN at the midpoint and end of chemotherapy and 1 year after chemotherapy. The incidence of CIPN was assessed using the Common Terminology Criteria for Adverse Events (CTCAE), Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), Patient Neurotoxicity Questionnaire (PNQ), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-NTX). The CTCAE is a clinician-based grading system that uses a 5-point scale to quantify the severity of both sensory and motor components of CIPN, and a score of ≥ 2 is considered indicative of CIPN; the PRO-CTCAE has a similar function with CTCAE but is patient-reported [22–24]. The PNQ is a self-administered questionnaire that collects diagnostic information from patients with CIPN, with grade C (on the scale A–E) indicative of moderate symptoms [25]. Because the CTCAE and PNQ were found to be positively correlated [26], this study defined CIPN as having a CTCAE grade ≥ 2 or a PNQ grade ≥ C. The FACT/GOG-NTX is a questionnaire that yields an aggregate score on the basis of an assessment of patient-reported peripheral neuropathic symptoms [27]. CIPN is defined as a reduction of more than 10% in FACT/GOG-NTX score between two consecutive time points, or a reduction of ≥ 5 points from baseline to 12 weeks [14, 28, 29]. QoL following chemotherapy was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), FACT/GOG-NTX and Patient-Reported Outcomes Measurement Information System 29-item Health Profile (PROMIS-29). The EORTC QLQ-C30 is a cancer-specific questionnaire that evaluates physical, psychological, and social functions in patients [30]. The PROMIS-29 is a validated tool assessing various aspects of health, such as pain, fatigue, physical function, depression, anxiety, and social function [31]. Regarding symptoms of neuropathy, a patient-reported questionnaire, EORTC QLQ-CIPN twenty-item scale (CIPN20), was adopted for evaluation [32].

Statistical analysis

Data were analyzed using Review Manager version 5.4 (Cochrane Collaboration, Oxford, UK). Data on incidence and dose reduction rates were dichotomous, and the effect sizes of the outcomes are reported as risks ratios (RR). QoL following chemotherapy was analyzed using standardized mean difference (SMD) values. Random-effects model was utilized in all analyzes [33]. The precision of each effect size was reported using a 95% confidence interval (CI). Studies without sufficient clinical and methodological similarity were excluded from data pooling. To evaluate statistical heterogeneity, we employed the I^2 test, which measures the proportion of outcome variability attributable to differences between the studies.

Results

Characteristics of the trials

The study selection process is illustrated in Fig. 1. The search strategy initially yielded 1,203 articles, of which 241 were duplicates and 921 were irrelevant. We reviewed the full text of 41 articles and subsequently excluded 6 abstracts, 5 reviews, 1 protocol, 2 surveys. 4 articles were excluded because they did not meet the inclusion criteria. Of the remaining 23 articles, 6 were duplicate reports and therefore excluded, leaving 17 studies eligible for inclusion in the meta-analysis.

Table 1 summarizes the characteristics of the included trials, published between 2013 and 2024, with sample sizes ranging from 21 to 1,548 participants. Of the 17 trials, 13 involved patients with breast cancer, 1 with digestive system malignancy, 1 with gynecologic cancer, and 2 with multiple cancer types, including colorectal, prostate cancer, and sarcoma. Patients received paclitaxel in 12 trials, with 6 trials using a regimen of 12 cycles of 80 mg/m2 weekly. Other trials involved docetaxel and oxaliplatin. Cryotherapy was primarily administered using frozen gloves and socks, except for three trials which used hilotherapy cooling [34], bags of crushed ice [35], and self-administered cooling [36]. Most trials investigated CIPN incidence, with sensory and motor CIPN analyzed in five and three studies, respectively. Dose reduction or cessation rates were provided in six trials, and QoL following chemotherapy was evaluated in five trials. Adverse events, tolerability, and severity of neuropathy were assessed in several trials.

Table 2 summarizes the methodological quality of the included studies. All RCTs had a low risk of bias in allocation and measurement. Five trials had some concerns due to deviations from the intended interventions, and notable missingness was observed in two trials [37, 38]. Incomplete reporting resulted in some concerns in two trials [38, 39]. Among NRCTs, one trial had a moderate risk of overall bias due to confounding factors, classification, deviation from intended intervention, and selection of reported results [40]. Another trial had moderate risk due to allowing the control group to receive cryotherapy after chemotherapy started [41]. One trial was rated as having a moderate risk of bias due to the randomization process (having an unspecified historical cohort) and notable

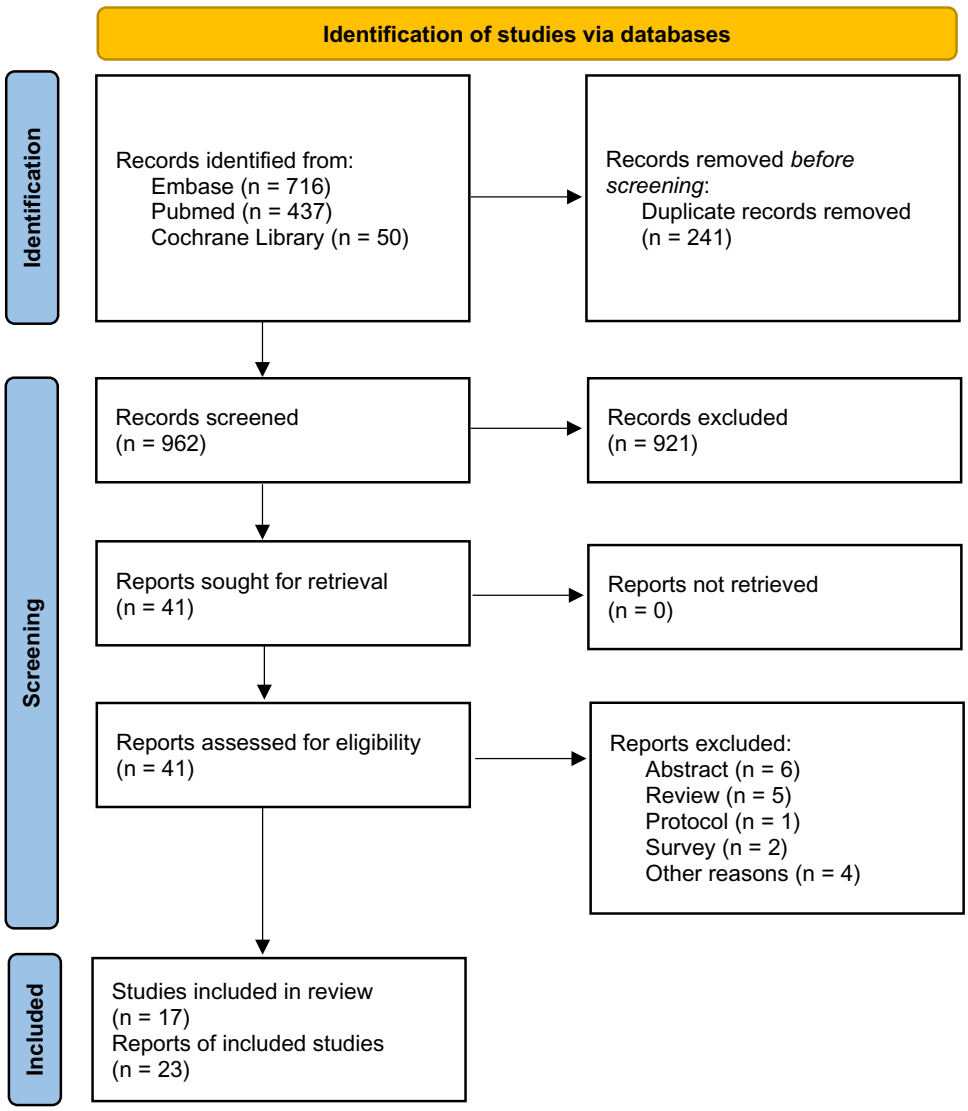

Fig. 1 Study selection process

missingness [42]. One trial had moderate selection bias and moderate bias in classification due to its retrospective nature and self-administered intervention [36].

Incidence of CIPN

The incidence of CIPN was measured in 11 trials, 6 of which evaluated overall CIPN by using the CTCAE [36, 42], PRO-CTCAE [34], FACT-NTX [39], and FACT/GOG-NTX [14, 29]. These six trials provided data on CIPN incidence at the end of chemotherapy; three also provided midpoint data, and one provided data more than 1 year after chemotherapy. Cryotherapy significantly reduced the incidence of CIPN at the midpoint and end of chemotherapy, with RRs of 0.23 (95% CI = 0.13 to 0.43) and 0.54 (95% CI = 0.33 to 0.88), respectively (Fig. 2). The incidence of CIPN 1 year after chemotherapy was lower in patients receiving cryotherapy, but not significantly different from the control group (RR = 0.43, 95% CI = 0.13 to 1.41). The total RR across all time points was 0.39 (95% CI = 0.27 to 0.58), demonstrating the prophylactic efficacy of cryotherapy. Moderate heterogeneity was observed across studies ($I^2 = 54.1\%$).

We investigated the association between different chemotherapeutic agents and CIPN incidence. Trials were categorized based on whether patients received a taxane-based agent or oxaliplatin (Fig. 3). Cryotherapy significantly reduced the incidence of TIPN at the midpoint and end of chemotherapy, with RRs of 0.25 (95% CI = 0.13 to 0.46) and 0.51 (95% CI = 0.27 to 0.94), respectively. Cryotherapy showed a tendency to reduce OIPN incidence, although this result did not reach statistical significance, with RRs of 0.06 (95% CI = 0.00 to 1.10) at the midpoint and 0.67 (95% CI = 0.39 to 1.15) at the end of

Table 1 Characteristics of included trials

Author [year]	Inclusion Criteria	Number of patients (% male)	Age, years, mean ± SD	Chemotherapy regimen	Intervention	Outcome assessment (timepoint)
RCTs (11)						
Accordino [29]	≥ 18 y, breast cancer	E1: 20 (0) E2: 22 (0) E3: 21 (0)	E1: 57.5 ± 15.3 E2: 53.5 ± 14.7 E3: 52.4 ± 12.6	Docetaxel, 3-weekly; or Paclitaxel weekly	E1: standard care + NatraCure gloves and socks with gel packs frozen at − 25 to − 30 °C E2: standard care + Sigvaris Secure Armsleeves Gloves and Gauntlet, providing 20–30 mmHg of compression E3: standard care + placebo with loose gloves/ socks (all applied 15 min before until 15 min after chemotherapy)	FACT-NTX; comfort/ satisfaction/ adherence; QoL; sensory perception; taxane toxicity (pre, 12 weeks)
Beijers [44]	All cancer	E: 90 (43) C: 90 (43)	E: 59.7 ± 9.7 C: 60.2 ± 9.8	Oxaliplatin, docetaxel, and paclitaxel	E: standard care + Elasto-Gel hypothermia gloves at − 20 °C, 15 min before until 15 min after chemotherapy C: standard care	CIPN20; QLQ-C30; NRS (pre, 3 cycles, end, 6 months after completion)
Chitkumarn [14]	≥ 18 y, gynecological cancer	E: 39 (0) C: 40 (0)	E: 57.59 ± 11.23 C: 55.45 ± 13.21	Paclitaxel, 175 mg/m^2, 3 h, 3-weekly × 6	E: standard care + 10 to 20 °C frozen gloves and socks, 15 min before until 15 min after chemotherapy C: standard care	Thai-version FACT/GOG-Ntx (each cycle, 1 month after completion)
Coolbrandt [34]	≥ 18 y; digestive system malignancy	E: 39 (66.7) C: 38 (55.3)	E: 65.03 ± 11.0 C: 61.6 ± 10.5	Oxaliplatin, 85 mg/m^2 2-weekly × 12; or 130 mg/m^2 3-weekly × 8	E: standard care + Hilotherm Chemocare hand and foot cooling device at 11 °C, 30 min before until 30 min after chemotherapy C: standard care	G2NF with PRO-CTCAE; dose reduction (12 weeks, 24 weeks); EORTC QLQ-CIPN20; (baseline, 6 weeks, 12 weeks, 18 weeks, 24 weeks)
Griffiths [37]	≥ 18 y; breast cancer	29 (0)	50.30 ± 25.73	Paclitaxel weekly × 12	E: standard care + Elasto-Gel gloves and socks at − 25 to − 30 °C, 15 min before until 15 min after chemotherapy C: standard care	NPSI; BPI; QST (pre, 1 week, 5 weeks, 9 weeks, end, 2 weeks after completion)
Jue [38]	Breast cancer	E: 24 (0) C: 24 (0)	E: 50.64 ± 11.82 C: 55.85 ± 12.61	1 h paclitaxel weekly × 12	E: standard care + Elasto-Gel frozen mitts & slippers at − 20 to − 24 °C, 15 min before until the end of chemotherapy C: standard care	CTCAE; FACT-Taxane questionnaire (weekly × 12, 1 month after completion)

Table 1 (continued)

Author [year]	Inclusion Criteria	Number of patients (% male)	Age, years, mean ± SD	Chemotherapy regimen	Intervention	Outcome assessment (timepoint)
Ng [13]	≥ 21 y; breast cancer	E: 21 (0) C:17 (0)	E: 56.4 ± 8.1 C: 53.6 ± 7.6	Paclitaxel, 80 mg/m^2, > 1 h, weekly × 12	E: standard care + Elasto-Gel hypothermia gloves and socks at − 20 to − 10 °C, 15 min before until 15 min after chemotherapy C: standard care	PRO Questionnaire (PNQ, CIPN20), EORTC QLQ C30, NCS, SSR
Ruddy [35]	Breast cancer; ECOG 0 or 1	E: 21 (5) C: 21 (0)	E: 51.2 ± 8.75 C: 56.8 ± 13.52	Paclitaxel, 80 mg/m^2, weekly × 12	E: standard care + bags of crushed ice on hands and feet, 15 min before until 15 min after chemotherapy C: standard care	APSSSQ; CTCAE; EORTC QLQ CIPN-20 (pre, weekly × 12, 1 month to 6 months after completion)
Shigematsu [39] [2023]	≥ 20 y; breast cancer; ECOG 0 or 1	E: 22 (0) C: 22 (0)	NA	Paclitaxel, 80 mg/m^2, weekly × 12	E: standard care + Elasto-Gel frozen gloves and socks at − 20 °C, 15 min before until 15 min after chemotherapy C: standard care	FACT-Ntx; PNQ; CTCAE; FACT-Taxane (pre, 3 weeks, 6 weeks, 9 weeks, end)
Sundar [47]	21–80 y; breast cancer	E1: 20 (0) E2: 13 (0)	E1: 50.2 ± 27.92 E2: 52.08 ± 29.9	Paclitaxel, 80 mg/m^2	E: standard care + 22 °C continuous coolant during chemotherapy C: standard care	NCS (pre, 1 month, end, 3 months after completion); TNS; VAS; CTCAE (every 3 weeks)
Xu [45]	Breast cancer	E: 42 (0) C: 80 (0)	E: 49 ± 11.4 C: 49.03 ± 10.7	Carboplatin, docetaxel, and paclitaxel	E: standard care + frozen gloves and socks at − 20 °C, 15 min before until 15 min after chemotherapy C: standard care	CIPNAT; EORTC QLQ-C30; CTCAE (pre, 7 days after completion)
NRCTs (6)						
Eckhoff [40]	Breast cancer	E: 686 C: 862	NA	D100 or D75, 3-weekly × 6	E: standard care + frozen gloves and socks at − 18 °C, 15 min before until 15 min after chemotherapy C: standard care	CTCAE
Hanai [43]	Breast cancer; ECOG 0 or 1	40 (0)	56.0 ± 13.8	Paclitaxel, 80 mg/m^2, 1 h, weekly × 12	E: standard care + Elasto-Gel frozen gloves and socks, 15 min before until 15 min after chemotherapy C: standard care	CIPN; vibration perception; performance speed; PNQ; (pre, before every cycle, end)
Rosenbaek [2019]	Breast cancer	E: 96 (0) C: 119 (0)	E: 55.9 ± 6.0 C: 58.6 ± 5.9	Paclitaxel, 80 mg/m^2, 1 h, weekly × 9	E: standard care + Elasto-Gel frozen gloves and socks at − 20 °C, 15 min before until 15 min after chemotherapy C: standard care	CTCAE (pre, before every cycle)

Table 1 (continued)

Author [year]	Inclusion Criteria	Number of patients (% male)	Age, years, mean ± SD	Chemotherapy regimen	Intervention	Outcome assessment (timepoint)
Sato [42]	Gynecologic cancer	E: 40 (0) C: 142 (0)	E: 59.7 ± 11.5 C: 56.5 ± 10.4	Paclitaxel, 150–175 mg/m^2, 3 h, 3-weekly × 6	E: standard care + Elasto-Gel frozen mitts and slippers at − 30 °C for 3 h C: standard care	CTCAE (pre, 3 weeks, 6 weeks, 9 weeks, 12 weeks, 3 weeks after completion)
Shimanuki [36]	≥ 20 y; breast cancer	E: 26 (0) C: 64 (0)	E: 53.86 ± 36.08 C: 53.06 ± 37.16	Paclitaxel, 80 mg/m^2, weekly × 12	E: standard care + self-administered cryotherapy, hands and feet C: standard care	CTCAE (post), dose reduction due to PN
Yang [2022]	≥ 20 y; breast cancer; receive paclitaxel for the first time	21 (0)	56.52 ± 10.98	Paclitaxel, 80 mg/m^2, weekly × 12	E: standard care + Elasto-Gel frozen gloves and socks at − 24 °C, 15 min before until 15 min after chemotherapy C: standard care	QLQ-CIPN20 (pre, 4 weeks, 8 weeks, 12 weeks, 4 weeks after completion)

D100: three cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by three cycles of docetaxel (100 mg/m^2)

D75: six cycles of cyclophosphamide (600 mg/m^2) and docetaxel (75 mg/m^2)

APSSSQ: Acute Pain Syndrome Symptom Summary Questionnaire; C: control group; CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item scale; CIPNAT: Chemotherapy-Induced Peripheral Neuropathy Assessment Tool; CTCAE: Common Terminology Criteria for Adverse Events; E: Experimental group; ECOG: Eastern Cooperative Oncology Group; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; G2NF: Grade ≥ 2 neuropathy-free rate; NA: not available; nab-PTX: Nanoparticle albumin-bound PTX; NCS: Nerve conduction study; PNQ: Patient Neurotoxicity Questionnaire; PRO: Patient Neurotoxicity Questionnaire; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAS: Shivering Assessment Scale; STS: Subjective Tolerance Scale; TNS: Total neuropathy score; VAS: visual analog pain scale

Table 2 Risk of bias assessment of included trials

Study	Allocation bias	Performance bias	Attrition bias	Measurement bias	Reporting bias	Overall
Accordino [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Beijers [44]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chitkumarn [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Coolbrandt [34]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Griffiths [37]	Low risk	Some concerns	High risk	Low risk	Low risk	High risk
Jue [38]	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Some concerns
Ng [13]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Ruddy [35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shigematsu [39]	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
Sundar [47]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xu [45]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

		Eckhoff [40]	Hanai [43]	Rosenbaek [2019]	Sato [42]	Shimanuki [36]	Yang [2022]
Preintervention	Bias due to confounding	Moderate	Low	Low	Low	Low	Low
	Selection bias	Low	Low	Low	Moderate	Moderate	Low
At intervention	Bias in classification of intervention	Moderate	Low	Moderate	Low	Moderate	Low
Postintervention	Deviation from intended interventions	Moderate	Low	Moderate	Low	Low	Low
	Bias due to missing data attrition	Low	Low	Low	Moderate	Low	Low
	Bias in measurement of outcomes	Low	Low	Low	Low	Low	Low
	Bias in selection of reported results	Moderate	Low	Low	Low	Low	Low
Overall		Moderate	Low	Moderate	Moderate	Moderate	Low

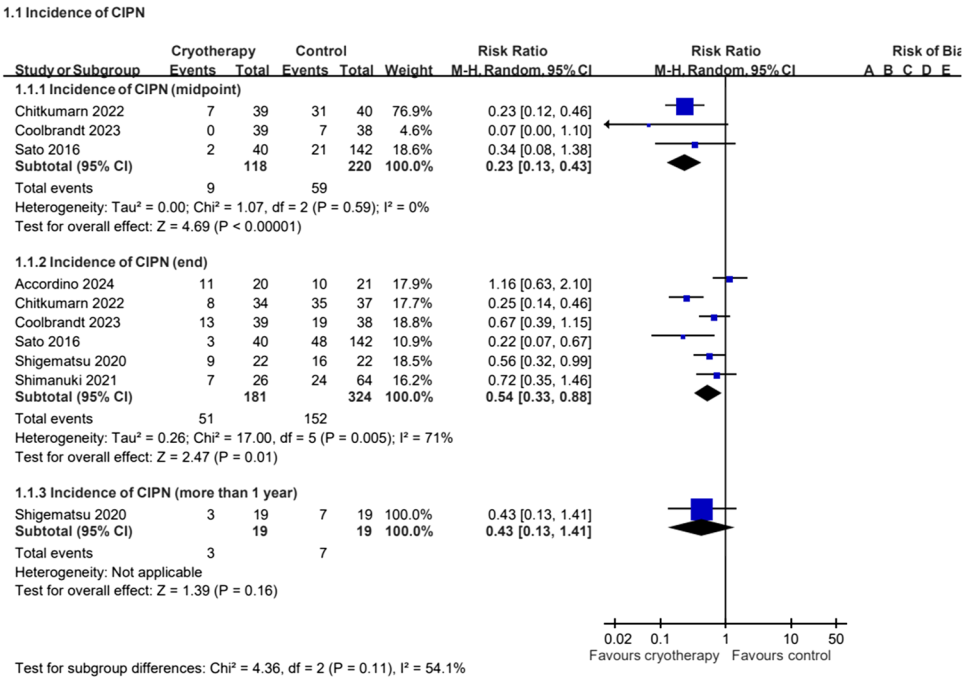

Fig. 2 Effects of cryotherapy on the incidence of CIPN at the midpoint (1.1.1) and end (1.1.2) of chemotherapy and more than 1 year after completion of chemotherapy (1.1.3)

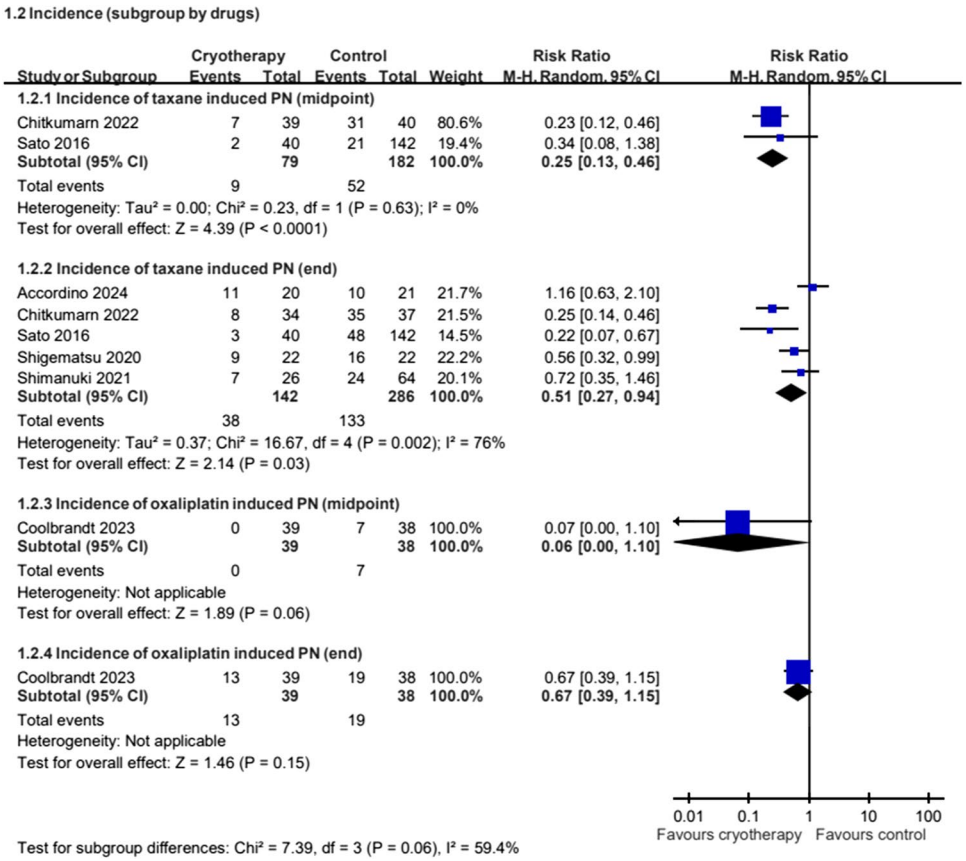

Fig. 3 Effect of cryotherapy on the incidence of TIPN at the midpoint (1.2.1) and end (1.2.2) of chemotherapy and on the incidence of OIPN at the midpoint (1.2.3) and end (1.2.4) of chemotherapy

chemotherapy. The RR for OIPN was 0.06 (95% CI = 0.00 to 1.10) at the midpoint and 0.67 (95% CI = 0.39 to 1.15) at the end of chemotherapy. However, the difference in OIPN incidence between the groups was not significant due to the limited number of trials available for pooling. Significant intertrial heterogeneity was noted regarding the incidence of TIPN at the end of chemotherapy ($I^2 = 76\%$).

Cryotherapy demonstrated a significant reduction in the incidence of CIPN in patients with gynecological cancers, with the relative risk (RR) being 0.24 (95% CI = 0.14 to 0.41; Figure S1). However, its preventive effects in patients with breast cancer and digestive system malignancy were not statistically significant, with RRs being 0.77 (95% CI = 0.50 to 1.20) and 0.67 (95% CI = 0.39 to 1.15), respectively. This analysis exhibited low heterogeneity across the trials within each subgroup, with an I^2 value of 33% for breast cancer and 0% for gynecological cancer (Figure S1).

Incidence of sensory and motor CIPN

Five studies provided data on sensory CIPN incidence, with three also providing data on motor CIPN incidence [13, 35, 39]. Sensory and motor CIPN symptoms were measured at the end of chemotherapy in each trial. The incidence of sensory CIPN was significantly lower in the cryotherapy group than in the control group, with an RR of 0.67 (95% CI = 0.49 to 0.92; Fig. 4). However, the trial with the highest proportion of participants had moderate risk of bias due to unclear information [40]. For motor CIPN, the difference in incidence between groups was not significant (RR = 0.28; 95% CI = 0.07 to 1.17). Low heterogeneity was found between trials for both subgroup analyses, with overall heterogeneity at 14% ($I^2 = 30\%$ for sensory CIPN and 0% for motor CIPN).

Dose reduction rate

Dose reduction rates were recorded in six trials [32–34, 39–41], with five measuring dose reductions due to CIPN only, and one including unspecified reasons [35]. No significant difference in dose reduction rate was found between the cryotherapy and control groups (RR = 0.97; 95% CI = 0.77 to 1.23; Figure S2). Low heterogeneity between trials was observed ($I^2 = 7\%$). One NRCT was excluded from pooling analysis due to significant deviations from the intended intervention protocol [41]. The study revealed that in the control group, there was a 9% CIPN-related dose reduction rate and a discontinuation proportion of 30%, whereas in the intervention group, these rates were 3% and 21%, respectively.

Quality of life

Five trials compared QoL between the cryotherapy and control groups, using EORTC QLQ-C30, PROMIS-29, and FACT/GOG-NTX scores [13, 14, 29, 44, 45]. Four trials indicated better overall QoL following chemotherapy for patients receiving cryotherapy. Significant improvements in global QoL were found in three trials using EORTC QLQ-C30 scores, with two trials also reporting higher physical functioning scores. In the Thai study, FACT/GOG-NTX scores were significantly better in the cryotherapy group after the second chemotherapy cycle, lasting until a 1-month follow-up [14]. In the trial employing PROMIS-29, no significant differences were observed

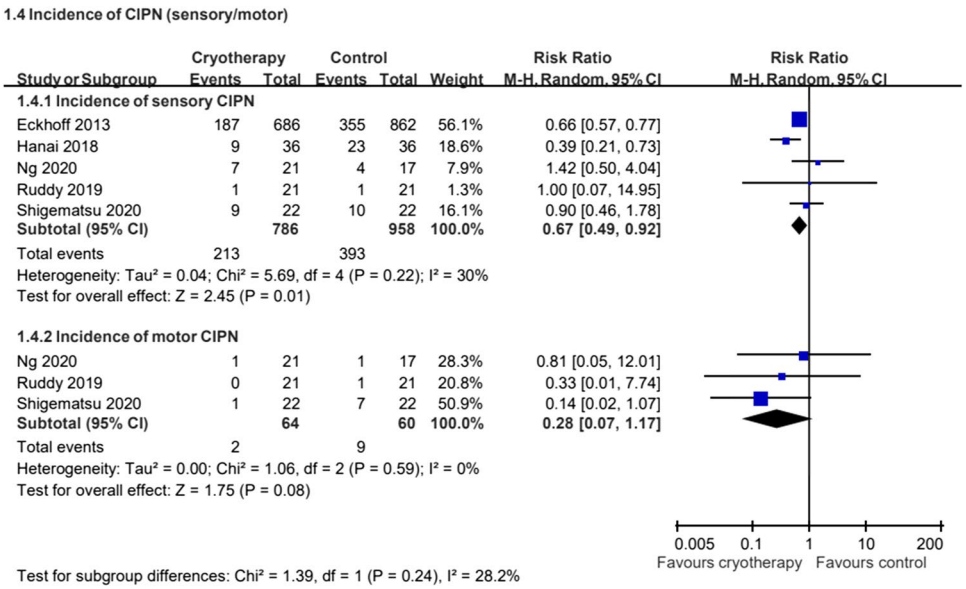

Fig. 4 Effects of cryotherapy on the incidence of sensory and motor CIPN

in the change from baseline to week 12 between participants receiving cryotherapy and those receiving a placebo [29]. Due to variation in the format of the results provided, the pooling analysis could only include data from two trials (Figure S3). Cryotherapy significantly improved global QoL scores following chemotherapy (SMD = 1.43; 95% CI = 0.50 to 2.36), with significant heterogeneity ($I^2 = 87\%$).

Severity of neuropathic symptoms

Six trials evaluated the severity of neuropathic symptoms, with four demonstrating positive effects of cryotherapy in reducing symptoms such as numbness, tingling, pain, and sensitivity to cold [13, 34, 44, 46]. Three trials provided scores for CIPN20 subscales (sensory, motor, and autonomic), with overall outcomes favoring cryotherapy [13, 44, 46]. One trial showed significant improvements in autonomic function at the 6-month follow-up after paclitaxel chemotherapy [13]. Another trial reported greater preservation of sensory, motor, and autonomic functions in the cryotherapy group, with symptom relief for "tingling fingers or hands" and "difficulty opening jars or bottles" [44]. In a Taiwanese trial, significant improvements in sensory symptoms were observed at all time points, with motor symptoms improving at the eighth week of treatment and 4-week follow-up [46].

Adverse events due to cryotherapy

Six trials provided data on adverse events, with three reporting mild and non-permanent events such as hypothermia-induced pain, sensory abnormalities, and erythema [13, 39, 44]. Most adverse events resolved promptly during or after cryotherapy, and pooling was not possible due to missing data on the exact number of events.

Cryotherapy tolerability

Cryotherapy tolerability was measured in eight trials. Five trials reported generally good tolerance levels, while three reported poorer tolerability. In Sundar's study, continuous-flow hypothermia showed high tolerability. Studies by Ruddy and Coolbrandt indicated favorable tolerability, and Accordino's study reported 75% satisfaction with cryotherapy. Hanai's study had no dropouts due to cold intolerance. However, Beijers' study reported a mean pain score of 3.1, with 34.4% discontinuing due to discomfort. In Griffiths' study, 34% dropped out due to cold intolerance, and Ng's study showed temporary suspension due to cold intolerance in 80.9% of participants.

Effect of cryotherapy on nerve conduction

Nerve conduction studies, including sensory nerve action potential and compound motor action potential (CMAP), were assessed in two studies [13, 47]. No significant differences in sensory nerve action potential parameters were discovered between the groups. CMAP amplitude was preserved to a slightly greater degree in the cryotherapy group than in the control group, but the difference was not significant. However, Ng's study identified statistically lower peroneal CMAP conduction velocity at 6 months after paclitaxel-based chemotherapy. The study of Accordino assessed sensory perception with a tuning fork vibrating on bilateral interphalangeal joints, which revealed diminished sensation in 64.3% and 50% participants receiving cryotherapy and placebo, respectively [29]. No significant strength of cryotherapy was demonstrated in objective assessing tools, primarily due to the limited availability of such assessments across trials.

Discussion

Our findings demonstrate the significant efficacy of cryotherapy in preventing CIPN, as indicated by the incidences of overall CIPN, sensory CIPN and global QoL following chemotherapy. Cryotherapy was also found to have benefits in preventing motor CIPN and alleviating the neuropathic symptoms, which further minimizes the need to reduce dosage, although these findings did not achieve statistical significance. No severe adverse events or lasting discomfort were reported, with some cases of temporary erythema and sensory abnormality observed. However, intolerance to hypothermia poses a challenge to the widespread adoption of cryotherapy. Participants' tolerance varied across the trials, possibly due to differences in cooling strategies.

Given the prevalence of cancer and the necessity of chemotherapy, CIPN affects millions of people worldwide each year [48]. This study primarily focused on taxanes and platinum-based drugs, known for their high neurotoxicity. Although the exact mechanism of CIPN remains unclear, studies have associated CIPN with oxidative stress, mitochondrial dysfunction, and elevation of proinflammatory cytokines [48, 49]. Taxanes, as microtubule-stabilizing agents that prevent mitosis of cancer cells, inevitably alter the dynamics of microtubules, thereby leading to axonal degeneration [50]. Moreover, damage to mitochondria causes oxidative stress and increases the production of reactive oxygen species, triggering a self-amplifying apoptotic process of demyelinization and inflammation [51]. Taxanes also lead to hyperexcitability of peripheral neurons and facilitate pain signaling by affecting ion channel function [52, 53]. As for platinum drugs, their neurotoxicity is hypothesized to be a result of an accumulation of platinum adducts in the dorsal root ganglion (DRG) and trigeminal ganglion [54].

Exposure to platinum-based drugs has been found to upregulate transient receptor potential channels in DRG, and this process may be associated with cold hyperalgesia [55]. Our results support the adoption of cryotherapy during infusion of taxanes-based chemotherapy, while its efficacy in preventing OPIN remains unclear. This finding may be attributed to the suboptimal site of cryotherapy application. Research has emphasized the accumulation of taxanes and oxaliplatin in DRG [54, 56]. A study employing low-back hypothermia in a rat model successfully alleviated paclitaxel-induced peripheral neuropathy by inhibiting the activation of astroglia and microglia in the spinal cord and decreasing the local concentration of paclitaxel [57]. Another study demonstrated that oral cryotherapy, which we hypothesize functions by cooling the trigeminal ganglion, effectively reduces the risks of oral thermal hyperalgesia and OIPN [58]. These findings suggested the potential efficacy of cryotherapy at ganglion sites.

Cryotherapy works by causing vasoconstriction and limiting regional toxicity perfusion, which helps prevent axonal degeneration and mitochondrial dysfunction [50, 59]. This mechanism is similar to that used by the DigniCap scalp cooling system for the prevention of alopecia after chemotherapy [60]. Of the 17 trials included in this study, 13 involved the use of frozen gloves and socks, and 2 involved the use of a continuous cooling system. Elasto-Gel frozen gloves and socks have been widely adopted in recent studies, which are typically initiated 15–30 min prior to chemotherapy infusion, replaced once during the session to maintain the temperature, and concluded 15–30 min after the end of chemotherapy [37–39]. Despite its convenience, cryotherapy is not always well tolerated. A survey conducted among Multinational Association of Supportive Care in Cancer members revealed that participants were worried about insufficient evidence (53.5%), logistical issues (34.85%), and patient discomfort (23.4%) regarding the use of cryotherapy for CIPN prevention [61]. Patient discomfort arises from inappropriate regional cooling strategies that involve excessively low temperatures leading to intolerance and high drop-out rates [37, 44]. To address this issue, continuous-flow cooling methods offer steady hypothermia and are better tolerated compared with the intermittent hypothermia provided by Elasto-Gel [47, 60, 62, 63]. Hilotherm, a closed-loop system covering on extremities that allowed coolant to circulate at a temperature of 10 °C, was demonstrated in a pilot study to provide better tolerance and lower dose reduction rates due to CIPN [64]. Additionally, research also found that convective cooling at 19 °C can reduce blood flow to 53–60%, which underlined the strengths of convective cooling [67, 67]. Although a pooling analysis comparing frozen mittens and continuous cooling is not feasible due to limited sample size in our study, we strongly encourage more investigation into the development of innovative continuous cooling devices.

The results of our study are consistent with those of other studies regarding the prophylactic effects of cryotherapy against TIPN. Furthermore, we investigated the severity of neuropathic symptoms, QoL, adverse events and tolerability of cryotherapy, which were crucial in clinical decision-making. As the efficacy of cryotherapy has been established in this study, further optimization necessitates immediate detection of CIPN progression. However, current diagnosis of CIPN relies predominantly on subjective assessments, lacking a standardized measure. Recent studies found that computed tomography is reliable in assessing DRG volume, which strongly correlated to the administrating dose of oxaliplatin in a longitudinal assessment [67]. Another study using MRI also highlighted that DRG hypertrophy was a significant correlate of the sensory neuropathy in OIPN patients, with peripheral nerves exhibiting minor alterations in morphology [67]. The utilization of DRG volume as a prospective marker for the early identification of CIPN may facilitate the timely reassessment of medication dosages. The progression of imaging technology presents an opportunity to enhance the prevention of CIPN through tailored cryotherapy interventions and personalized dosage adjustments.

In our meta-analysis, high heterogeneity was observed regarding the incidence of CIPN at the end of chemotherapy. To address this heterogeneity, we conducted a subgroup analysis to examine the effects of cryotherapy on TIPN versus OIPN. However, even after this subgroup analysis, significant heterogeneity remained in the incidence of TIPN at the end of chemotherapy ($I^2 = 61\%$). This may be attributed to differences in cooling methods and outcome measurements between trials. The cooling devices employed in the trials varied from frozen gloves and socks to hilotherapy cooling and self-administered hypothermia, resulting in a wide range of temperature changes. More trials with larger samples are needed for more comprehensive subgroup analyses.

The strengths of our meta-analysis include the comprehensiveness of the search for eligible trials, systematic and transparent selection of eligibility criteria, careful evaluation of study quality, and rigorous analytical approach. This study provides updated insights, elucidating various dimensions of cryotherapy's efficacy and incorporating advancements in technological methodologies. However, the study also has limitations. First, the sample size was small. Second, NRCTs may have introduced bias. Third, poor compliance in some trials has led to high dropout rate, which reduced the robustness of our analysis. Lastly, most studies were terminated soon after the end of chemotherapy, resulting in a lack of long-term data.

Conclusion

This meta-analysis provides evidence supporting the efficacy of cryotherapy in the prevention of CIPN, as indicated by incidences of CIPN and patients' QoL. Moreover, it also

provides relief from neuropathic symptoms following chemotherapy. Patients receiving chemotherapy are recommended to adopt cryotherapy though tolerance to cold varies across individuals and different cooling strategies. Cryotherapy is recommended in the form of frozen gloves and socks or continuous-flow cooling, from at least 15 min before the start of chemotherapy until 15 min after the end of chemotherapy. Frozen gloves and socks should be replaced once to maintain hypothermia during infusion of the therapeutic agent. Despite concerns about variation in the clinical application of cryotherapy in this study, its efficacy in CIPN prevention and its minimal risk of adverse events mean that cryotherapy should be investigated further.

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