# Feet Cooling As a Preventive Strategy against Chemotherapy-Induced Peripheral Neuropathy in Advanced Breast Cancer Patients: A Randomized Clinical Trial

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## Abstract

**Continuous foot cooling during taxane infusion significantly reduced chemotherapy-induced peripheral neuropathy in breast cancer patients. This noninvasive, well-tolerated strategy may improve treatment adherence and quality of life.**

**Background:** Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating adverse effect of taxane-based chemotherapy, often persisting long after treatment completion. This study evaluates the efficacy of continuous foot cooling with an adjustable temperature wrap during taxane infusion to prevent CIPN in breast cancer patients. **Methods:** In this open-label randomized controlled trial, 120 patients with stage I to III breast cancer undergoing paclitaxel-based chemotherapy were randomly assigned to an intervention group receiving continuous feet cooling (13°C-16°C) initiated 30 minutes before and maintained until 15 minutes after chemotherapy infusion, alongside standard care, or to a control group receiving standard care alone. CIPN was assessed using the modified EORTC QLQ-CIPN20 questionnaire at 6 weeks ($t_1$), 12 weeks ($t_2$), and 3 months post-treatment ($t_3$). **Results:** Baseline characteristics were balanced between groups. The intervention group demonstrated significantly lower-limb CIPN scores compared to controls at all time points: week 6 ($21.58 \pm 5.89$ vs. $26.28 \pm 7.78$; $P < .001$), week 12 ($22.75 \pm 7.15$ vs. $28.56 \pm 6.99$; $P < .001$), and 3 months post-treatment ($19.73 \pm 5.90$ vs. $26.65 \pm 19.48$; $P < .001$). The number needed to treat (NNT) was 7, indicating a moderate protective effect. Foot cooling was well tolerated, with no differences in chemotherapy dose modifications. **Conclusion:** Continuous foot cooling during chemotherapy significantly reduces the incidence of CIPN and may improve treatment adherence. Larger multicenter trials are needed to validate these findings. **Clinical Trial Registration:** Iranian Registry of Clinical Trials (IRCT) number IRCT20231108059991N1.

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## Introduction

Breast cancer continues to represent a complex and highly prevalent health challenge, affecting millions globally.[1] Advances in early detection and treatment have significantly improved patient survival; however, many patients endure persistent treatment-related adverse effects.[2] Chemotherapy regimens containing taxane compounds represent standard care but are frequently associated with chemotherapy-induced peripheral neuropathy (CIPN), a debilitating condition that profoundly impairs functional status and quality of life.[2-4]

The development and severity of CIPN are influenced by a constellation of predisposing, precipitating, and perpetuating factors. Predisposing factors such as advanced age, genetic predispo-

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sition, and the presence of comorbidities, including diabetes mellitus or hereditary neuropathies, contribute to increased vulnerability. Precipitating factors primarily relate to the chemotherapy regimen itself, including the specific type of chemotherapeutic agent, cumulative dose, and treatment schedule. Furthermore, the concomitant administration of other neurotoxic agents can exacerbate neuropathic risk. Perpetuating factors, including depression, poor nutritional condition, and physical inactivity, may contribute to the persistence and worsening of symptoms. Collectively, these multifaceted factors underscore the complexity and heterogeneity inherent in the pathogenesis and clinical presentation of CIPN.[5-10]

CIPN affects 58% to 78% of patients treated with neurotoxic agents; notably, approximately 30% experience long-term disability, leading to impaired daily functioning, reduced independence, and compromised emotional well-being.[11,12] Clinical manifestations of CIPN include sensory symptoms (eg, altered temperature sensation, numbness, tingling, hypersensitivity), motor deficits (eg, muscle tremors or spasms), autonomic dysfunction (eg, neurogenic bladder dysfunction, constipation), and cranial nerve involvement.[2,13,14]

The pathophysiology of CIPN is complex, multifactorial, and not yet fully elucidated. It involves a dynamic interplay of diverse mechanisms, including oxidative stress, apoptotic signaling pathways, dysregulation of calcium homeostasis, axonal degeneration, and membrane remodeling, in conjunction with immune system activation and neuroinflammatory responses. Direct damage to peripheral neurons, and mitochondrial dysfunction are also key contributors to disease progression. For example, taxane chemotherapeutics disrupt microtubule dynamics critical for axonal transport, thereby precipitating axonal degeneration. Additionally, the activation of inflammatory cascades and alterations in ion channel expression exacerbate neuronal hyperexcitability, which underlies the neuropathic pain frequently experienced by CIPN patients.[10,15-19]

Despite numerous clinical trials, no standardized, evidence-based intervention exists for the prevention or effective treatment of CIPN, underscoring the urgent need for novel, cost-effective strategies.[5,11,14,20] Cryotherapy, or local cooling of the extremities during chemotherapy, has emerged as a promising nonpharmacological approach. Regulatory approval for scalp cooling to prevent chemotherapy-induced alopecia is based on the principle of vasoconstriction, which reduces drug delivery to hair follicles. By a similar mechanism, cooling the hands and feet may reduce peripheral nerve exposure to chemotherapeutic agents and mitigate metabolism and inflammation contributing to CIPN development.[14,21]

Although studies on extremity cooling report mixed outcomes, no consensus exists regarding optimal frequency, duration, or methodology.[13,14] The randomized controlled trials presented here evaluate the efficacy of continuous foot cooling in reducing the incidence of CIPN among breast cancer patients receiving weekly paclitaxel chemotherapy, aiming to establish robust evidence for this preventive intervention.

## Methods

### *Study Design and Participants*

This open-label, single-center, randomized controlled trial enrolled 120 patients with stage I to III breast cancer scheduled for weekly paclitaxel-based chemotherapy at Vasei Hospital, Sabzevar, between April 2023 and April 2025. The sample size was determined based on prior study by Leen et al. (2022).[22] Eligibility criteria included: age $< 75$ years, functional performance score $> 70\%$, receiving paclitaxel as part of chemotherapy regimen at the time of enrollment, signed informed consent, and willingness to use the cooling device. Patients were excluded if they had prior chemotherapy, peripheral neuropathy, cryoglobulinemia, melanoma, systemic lupus erythematosus, uncontrolled diabetes mellitus, or were taking medications masking CIPN symptoms, such as serotonin-norepinephrine reuptake inhibitors. Participants unwilling to participate in the study and to receive the cooling intervention were also excluded.

Ethical approval was obtained from the Sabzevar University of Medical Sciences Ethics Committee (IR.MEDSAB.REC.1402.074). The trial was registered with the Iranian Registry of Clinical Trials (IRCT20231108059991N1). Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

### *Randomization and Blinding*

Participants were randomized (1:1) using permuted blocks to intervention or control groups. Due to the nature of the foot cooling intervention, blinding of patients and clinicians was not feasible; however, outcome assessors were blinded to treatment allocation to reduce detection bias.

### *Cooling Device*

The limb cooling device (Sarma Behboud Sepanta Medical Industries, Iran) utilized a hermetic compressor to actively lower the temperature of a glycol-based coolant to a precise target of 10°C. Throughout the duration of paclitaxel treatment, the coolant temperature was stabilized within $\pm$ 1.5°C to ensure consistent thermal regulation. The chilled glycol was continuously circulated through insulated hoses, delivering coolant to polymer-based wraps specifically designed for foot application. These wraps incorporated engineered liquid channels to facilitate uniform heat transfer and were encased in a biocompatible fabric, optimizing patient comfort and safety (Figure 1). The cooling device were applied by the chemotherapy nurse approximately 30 minutes before paclitaxel administration and remained in place throughout the infusion. The use of the device did not significantly prolong the patients' chair time, as cooling was performed during the routine waiting period before chemotherapy initiation. Likewise, the additional nursing workload was minimal, as nurses only needed to fit the device and start the device.

An integrated microprocessor controlled and monitored the cooling process, offering real-time adjustments via a user-friendly color touchscreen interface accessible to trained personnel. Limb temperature was regulated indirectly by adjusting the coolant temperature, eliminating the need for complex skin temperature sensors while maintaining effective heat exchange. The device's performance was rigorously validated through experimental measurements and software simulations, confirming an estimated epidermal temperature range of 13°C to 16°C.

**Figure 1** Cooling device for temperature regulation. A) Foot wrap and B) Total device.


### *Intervention*

The intervention group received continuous bilateral foot cooling via a temperature-controlled foot wrap, which was initiated 30 minutes before the start of each paclitaxel infusion and maintained until 15 minutes after infusion completion, beginning with the very first course of chemotherapy. The hands served as intra-individual controls with no cooling applied. The control group received routine chemotherapy without cooling.

Paclitaxel dosing (80 mg/m² weekly, for 12 cycles) and other clinical decisions followed standard oncologic guidelines.

### *Outcome Measures and Assessments*

The primary endpoint was CIPN incidence and severity, assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy module (EORTC QLQ-CIPN20). This self-report instrument employs a 4-point Likert scale (1 = "not at all" to 4 = "very much") to measure sensory, motor, and autonomic symptoms. Scores range from 8 to 32 for upper limbs and 7 to 28 for lower limbs, with higher scores denoting greater neuropathy severity. The questionnaire's reliability (Cronbach's alpha $> 0.8$)[23,24] and validity have been established. Assessments were conducted at 3 time points: $t_1$: 6 weeks after chemotherapy initiation, $t_2$: 12 weeks (end of paclitaxel treatment), and $t_3$: 3 months post-treatment completion.

Patients with pre-existing peripheral neuropathy were excluded; hence, no baseline (time zero) CIPN assessment was performed. CIPN was evaluated prospectively at week 6 (t1), week 12 (t2), and 3 months after completion of chemotherapy (t3). In the intervention arm, foot cooling was initiated 30 minutes before the first paclitaxel infusion and continued during all subsequent cycles, until 15 minutes after infusion completion.

Intervention tolerability was assessed after each cooling session using a 5-point Likert scale (very uncomfortable, uncomfortable, neutral, comfortable, and very comfortable).

### *Statistical Analysis*

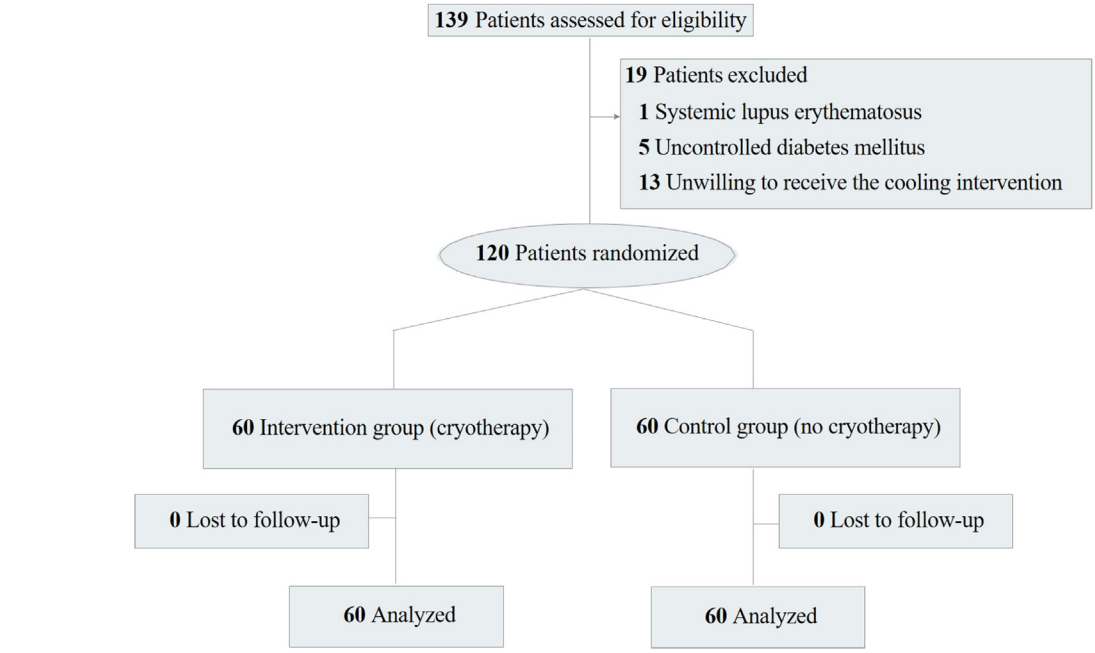
Baseline characteristics were summarized using means ± standard deviations for continuous variables and frequencies (percentages) for categorical data. Between-group comparisons of CIPN scores at each time point were performed using the Mann–Whitney U test for independent samples and the Friedman test for repeated measures. The number needed to treat (NNT) was derived as the reciprocal of the absolute risk reduction (ARR), calculated from the difference in the incidence of clinically significant CIPN between the intervention and control groups at the end of chemotherapy. A lower NNT indicates a greater preventive effect of the intervention. Statistical analyses were executed in SPSS v24 (SPSS Inc., Chicago, IL, USA), with significance set at $P < .05$.

## Results

Initially, 139 patients with breast cancer were screened for eligibility. Nineteen patients were excluded: one due to systemic lupus erythematosus, 5 due to uncontrolled diabetes mellitus, and thirteen who declined to continue with the cooling intervention. The remaining 120 patients who met the inclusion criteria were randomized equally into 2 groups: the intervention group ($n = 60$) and the control group ($n = 60$) (Figure 2). In the intervention group, foot cooling was delivered during each paclitaxel infusion. As all patients received 12 weekly cycles, the average duration of cooling was 12 weeks. The mean cumulative dose of paclitaxel was comparable between the intervention and control groups (960 mg/m² each, corresponding to 12 cycles of 80 mg/m²).

Comparative analysis of baseline characteristics revealed no statistically significant differences between the intervention and control groups in mean age ($P = .216$), molecular subtypes ($P = .257$), tumor location ($P = .126$), laterality ($P = .097$), or past medical history ($P = .855$). Additionally, disease stage, tumor grade, hormone receptor status (estrogen receptor (ER) and progesterone receptor (PR)), and human epidermal growth factor receptor 2 ($HER_2$) receptor status were similar between groups ($P = .166$,

**Figure 2** CONSORT flow chart illustrating the participants' progression through the clinical trial.




$P = .938$, $P = .532$, and $P = .067$, respectively), confirming effective randomization (Table 1).

The intervention group, which received continuous foot cooling, exhibited significantly lower CIPN scores compared to controls at all assessed time points (Table 2). At week 6 (t1), mean CIPN scores were 21.58 ± 5.89 versus 26.28 ± 7.78 ($P < .001$); at week 12 (t2), 22.75 ± 7.15 versus 28.56 ± 6.99 ($P < .001$); and at 3 months post-treatment (t3), 19.73 ± 5.90 versus 26.25 ± 19.48 ($P = .001$), for intervention and control groups, respectively.

Repeated-measures analysis demonstrated significant changes in foot CIPN scores over time within both groups ($P < .001$) (Table 3). Similarly, hand CIPN scores showed significant within-group temporal differences ($P < .001$) (Table 4); however, no significant differences were found between groups at any time point (Table 5).

Furthermore, significant differences between hand and foot CIPN scores were observed at all time points in both groups (Table 6). The calculated number needed to treat (NNT) was 7, indicating that 7 patients would need to receive foot cooling to prevent 1 additional case of clinically significant CIPN.

Patients in the cryotherapy group rated the intervention as neutral to very comfortable, and none requested discontinuation of cooling

## Discussion

CIPN is a frequent and dose-limiting adverse effect of paclitaxel treatment, significantly impacting patients' functional status and quality of life. The pathophysiology of paclitaxel-induced neuropathy is multifactorial, involving oxidative stress, axonal degeneration, and neuroinflammatory processes that contribute to sensory and motor symptoms. Current efforts to mitigate CIPN focus on neuroprotective strategies, including cryotherapy, which seeks to limit peripheral nerve exposure during chemotherapy administration.[25-28]

This randomized controlled trial demonstrated that continuous foot cooling significantly reduces CIPN scores in breast cancer patients undergoing paclitaxel-based chemotherapy. The intervention group showed lower CIPN severity at 6 weeks, 12 weeks, and 3 months post-treatment compared to controls and their own upper limbs. The number needed to treat (NNT = 7) further emphasizes foot cooling's clinical potential as an effective neuroprotective strategy.[13] These findings support the hypothesized mechanism whereby localized cooling induces vasoconstriction, limiting chemotherapeutic exposure to peripheral nerves and thereby mitigating neurotoxicity through reduced metabolism and inflammation.[29]

Importantly, cooling devices decrease CIPN manifestations both during chemotherapy and in the post-treatment period, thereby enhancing treatment tolerability and compliance. This effect has the potential to reduce chemotherapy dose delays or discontinuations, which could ultimately improve therapeutic outcomes. Moreover, by attenuating the persistence of neuropathy after treatment completion, foot cooling may contribute to better long-term quality of life in cancer survivors, who otherwise face ongoing pain, sensory disturbances, and functional impairments that adversely affect daily living and emotional well-being.[28,30-32]

As expected, the cooling intervention targeted only the feet, and no significant differences in hand CIPN scores were observed between groups. Notably, significant within-group differences between hand and foot CIPN scores across all time points suggest

**Table 1** General Characteristics of Study Participants

| | Intervention Group | Control Group | *P* Value |
|---|---|---|---|
| Age, mean ± SD, y | 48.55 ± 10.47 | 46.23 ± 9.92 | .216[a] |
| Molecular subtypes (n) | | | |
| $HER_2$-positive ($HR^-$ ($ER^-$, $PR^-$), $HER_2{}^+$) | 32 | 23 | .257[b] |
| Triple-negative ($HR^-$ ($ER^-$, $PR^-$), $HER_2{}^-$) | 6 | 8 | |
| Hormone receptor ($HR^+$ ($ER^+$and/or $PR^+$), $HER_2{}^-$) | 22 | 29 | |
| Tumor location (n) | | | |
| Central portion | 13 | 6 | .126[b] |
| Upper outer quadrant (UOQ) | 32 | 26 | |
| Upper inner quadrant (UIQ) | 5 | 10 | |
| Lower outer quadrant (LOQ) | 4 | 8 | |
| Lower inner quadrant (LIQ) | 6 | 10 | |
| Laterality (n) | | | |
| Right | 21 | 30 | .097[b] |
| Left | 39 | 30 | |
| Past medical history (n) | | | |
| Yes | 31 | 30 | .855[b] |
| No | 29 | 30 | |
| Disease stage (n) | | | |
| stage I | 7 | 12 | .166[b] |
| stage II | 35 | 25 | |
| stage III | 18 | 23 | |
| Tumor grade (n) | | | |
| Grade 1 (low grade) | 4 | 5 | .938[b] |
| Grade 2 (intermediate grade) | 30 | 29 | |
| Grade 3 (high grade) | 26 | 26 | |
| Hormone receptor status (n) | | | |
| Negative | 14 | 17 | .532[b] |
| Positive | 46 | 43 | |
| $HER_2$ receptor status (n) | | | |
| Negative | 27 | 17 | .067[b] |
| Positive | 33 | 43 | |

Abbreviations: ER = estrogen receptor; HR = hormone receptor; $HER_2$ = human epidermal growth factor receptor 2; PR = progesterone receptor.
[a] Obtained from independent sample test.
[b] Obtained from Pearson Chi-square test.

**Table 2** Comparison of Foot Cooling Efficacy Between Intervention and Control Groups Using Quality-of-Life Questionnaire Scores and the Mann–Whitney U Test

| | Intervention Group | Control Group | Difference In Means | *P* Value |
|---|---|---|---|---|
| EORTC QLQ-CIPN20 ($t_1$), mean ± SD | 21.58 ± 5.89 | 26.28 ± 7.78 | 4.7 | < .001* |
| EORTC QLQ-CIPN20 ($t_2$), mean ± SD | 22.75 ± 7.15 | 28.56 ± 6.99 | 5.81 | < .001* |
| EORTC QLQ-CIPN20 ($t_3$), mean ± SD | 19.73 ± 5.90 | 26.25 ± 19.48 | 6.52 | .001* |

Abbreviations: EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; $t_1$ = 6 weeks after chemotherapy initiation; $t_2$ = 12 weeks after chemotherapy initiation (end of paclitaxel treatment); $t_3$ = 3 months post-treatment completion.
* The asterisk represents a statistically significant difference ($P \leq .05$).

that paclitaxel-induced neuropathy predominantly begins in the lower limbs, consistent with previous reports that neuropathy often initiates distally and may present exclusively in the feet in some patients.[25,33]

The high tolerability of foot cooling in this study, with minimal impact on chemotherapy dosing, supports its feasibility for routine clinical use. As a simple, noninvasive approach, continuous foot cooling may effectively reduce the incidence of CIPN, promote treatment adherence, and ultimately enhance patients' quality of life.

In comparing our results to prior studies, heterogeneous findings highlight the complexity of cryotherapy's efficacy:

**Table 3** Evaluation of Foot Cooling Efficacy across Repeated Measurements Using Quality-of-Life Questionnaire Scores and The Friedman Test

| | EORTC QLQ-CIPN20 ($t_1$) mean ± SD | EORTC QLQ-CIPN20 ($t_2$) mean ± SD | EORTC QLQ-CIPN20 ($t_3$) mean ± SD | *P* Value |
|---|---|---|---|---|
| Intervention group | 10.30 ± 3.44 | 11.21 ± 3.76 | 9.80 ± 3.37 | < .001* |
| Control group | 14.66 ± 5.05 | 16.45 ± 5.45 | 13.36 ± 4.02 | < .001* |

Abbreviations: EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; $t_1$ = 6 weeks after chemotherapy initiation; $t_2$ = 12 weeks after chemotherapy initiation (end of paclitaxel treatment); $t_3$ = 3 months post-treatment completion.
* The asterisk represents a statistically significant difference ($P \leq .05$).

**Table 4** Assessment of Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Hands Over Multiple Time Points Using Quality-of-Life Questionnaire Scores and the Friedman Test

| | EORTC QLQ-CIPN20 ($t_1$) mean ± SD | EORTC QLQ-CIPN20 ($t_2$) mean ± SD | EORTC QLQ-CIPN20 ($t_3$) mean ± SD | *P* Value |
|---|---|---|---|---|
| Intervention group | 11.08 ± 3.32 | 11.98 ± 4.09 | 10.00 ± 2.88 | < .001* |
| Control group | 12.01 ± 3.80 | 12.88 ± 4.25 | 10.85 ± 3.87 | < .001* |

Abbreviations: EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; $t_1$ = 6 weeks after chemotherapy initiation; $t_2$ = 12 weeks after chemotherapy initiation (end of paclitaxel treatment); $t_3$ = 3 months post-treatment completion.
* The asterisk represents a statistically significant difference ($P \leq .05$).

**Table 5** Assessment of Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Hands Between Intervention and Control Groups Using Quality-of-Life Questionnaire Scores and The Mann–Whitney U test

| | Intervention Group | Control Group | Difference in Means | *P* Value |
|---|---|---|---|---|
| EORTC QLQ-CIPN20 ($t_1$), mean ± SD | 11.08 ± 3.32 | 12.01 ± 3.80 | 0.93 | .171 |
| EORTC QLQ-CIPN20 ($t_2$), mean ± SD | 11.98 ± 4.09 | 12.88 ± 4.25 | 0.9 | .105 |
| EORTC QLQ-CIPN20 ($t_3$), mean ± SD | 10.00 ± 2.88 | 10.85 ± 3.87 | 0.85 | .264 |

Abbreviations: EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; $t_1$ = 6 weeks after chemotherapy initiation; $t_2$ = 12 weeks after chemotherapy initiation (end of paclitaxel treatment); $t_3$ = 3 months post-treatment completion.

**Table 6** Comparison of Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Hands and Feet between Intervention and Control Groups Using Quality-of-Life Questionnaire Scores and the Mann–Whitney U test

| | Intervention Group (hands) | Intervention Group (feet) | Difference in Means | *P* Value |
|---|---|---|---|---|
| EORTC QLQ-CIPN20 ($t_1$), mean ± SD | 11.08 ± 3.32 | 10.30 ± 3.44 | 0.78 | < .001* |
| EORTC QLQ-CIPN20 ($t_2$), mean ± SD | 11.98 ± 4.09 | 11.21 ± 3.76 | 0.77 | < .001* |
| EORTC QLQ-CIPN20 ($t_3$), mean ± SD | 10.00 ± 2.88 | 9.80 ± 3.37 | 0.2 | .004* |
| | Control Group (Hands) | Control Group (Feet) | Difference in Means | *P* value |
| EORTC QLQ-CIPN20 ($t_1$), mean ± SD | 12.01 ± 3.80 | 14.66 ± 5.05 | 2.65 | .001* |
| EORTC QLQ-CIPN20 ($t_2$), mean ± SD | 12.88 ± 4.25 | 16.45 ± 5.45 | 3.57 | .003* |
| EORTC QLQ-CIPN20 ($t_3$), mean ± SD | 10.85 ± 3.87 | 13.36 ± 4.02 | 2.51 | .001* |

Abbreviations: EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; $t_1$ = 6 weeks after chemotherapy initiation; $t_2$ = 12 weeks after chemotherapy initiation (end of paclitaxel treatment); $t_3$ = 3 months post-treatment completion.
* The asterisk represents a statistically significant difference ($P \leq .05$).

Ruddy et al. (2019) evaluated hand and foot cooling with crushed ice in paclitaxel-treated patients and found no significant difference in sensory CIPN scores over 12 weeks, though cryotherapy was well tolerated.[34] Our results showing benefit with foot cooling may relate to methodological differences, such as continuous cooling a controlled temperature.

Ng et al. (2020) tested frozen gloves and socks but reported no significant improvements in neuropathy severity at 2 weeks post-treatment, with a delayed benefit for motor symptoms at 3 months. However, a high interruption rate due to cold intolerance (80.9%) likely reduced overall efficacy.[35] Our study's continuous foot cooling may provide improved tolerability and adherence by targeting 1 area and using controlled temperature.

Beijers et al. (2020) conducted a randomized trial with frozen gloves for various chemotherapies and found no significant difference in CIPN severity compared to controls, though some symptom mitigation and quality-of-life improvement were noted. Importantly, about one-third of patients discontinued due to discomfort.[36]

This underscores the need for patient-friendly cooling approaches; our results suggest continuous foot cooling may offer a better balance of efficacy and tolerability. Contrastingly, Yang et al. (2023) reported significant reductions in sensory and motor CIPN in the dominant hand with frozen gloves, reinforcing the potential for cryotherapy to prevent CIPN when well tolerated.[37,38]

Most recently, Michel et al. (2025) provided compelling evidence supporting localized interventions by comparing one-sided hand cooling (using a frozen glove) with compression (via tightly fitting surgical gloves) in breast cancer patients receiving taxane chemotherapy. Both interventions, applied to the dominant hand 30 minutes before, during, and after treatment, significantly reduced the incidence of high-grade CIPN, with cooling demonstrating a greater effect size. Approximately 6% of patients discontinued the study due to intolerance to the intervention.[11] In contrast, our study reported successful foot cooling without intolerance, suggesting that the choice of extremity and cooling modality may critically impact both efficacy and patient adherence.

Besides these pieces of evidence, a meta-analysis by Jia et al. (2021) of 9 trials ($n \approx 2250$) showed that cryotherapy significantly reduces the risk of grade $\geq 2$ sensory and motor sensory peripheral neuropathy in patients receiving taxanes, and more recently, a network meta-analysis by Chen et al. (2025) involving 13 studies (865 patients) demonstrated that cryotherapy—especially continuous cooling and frozen gloves—was associated with a substantial reduction in the incidence of chemotherapy-induced peripheral neuropathy compared to usual care.[39,40]

In terms of feasibility, the cooling devices were applied by nurses during the routine preinfusion period and remained in place throughout chemotherapy, without prolonging chair time or causing notable increases in nursing workload. This suggests that the intervention is practical even in busy infusion clinic settings.

This study has several limitations. The open-label design may have introduced performance bias, as neither participants nor healthcare providers were blinded to the intervention. Additionally, the single-center setting may restrict the generalizability of our findings; therefore, multicenter trials are warranted to validate these results across diverse clinical environments. One limitation of our study is that the control group did not receive a sham intervention (wrap without active cooling). This design would have allowed us to better isolate the specific effect of cooling from any potential placebo or mechanical effects of the wrap itself. Moreover, the long-term effects of foot cooling on CIPN remain unexamined, highlighting the need for future research to assess the durability and sustained impact of this intervention. Another limitation is the exclusion of other chemotherapeutic agents, which restricts the extrapolation of our findings to different treatment regimens, particularly those involving oxaliplatin, where cold hypersensitivity is a prominent clinical concern and warrants specific investigation regarding cooling device efficacy.

## Conclusion

This is the first randomized clinical trial to evaluate the efficacy of a cooling device with a constant temperature range for the prevention of CIPN. This approach significantly reduced the incidence of CIPN. Given its accessibility, cost-effectiveness, and high tolerability, this cryotherapy method holds promise for integration into routine clinical practice.

## Clinical Practice Points

- Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and persistent complication of taxane therapy that reduces quality of life and may compromise treatment adherence.
- This trial demonstrates that continuous foot cooling with an adjustable temperature wrap during taxane infusion significantly reduces the incidence and severity of CIPN.
- The intervention was safe, well tolerated, and did not interfere with chemotherapy administration or dosing.
- Implementation of foot cooling may provide oncologists with a practical, low-cost, and patient-friendly supportive care option.
- Larger multicenter studies are needed to confirm efficacy and facilitate integration into routine clinical practice.

## Funding

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## Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declaration on Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Sider (GPT-4.1 mini) to improve readability and language. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## Ethics Approval

Ethical approval was obtained from the Sabzevar University of Medical Sciences Ethics Committee (IR.MEDSAB.REC.1402.074). The trial was registered with the Iranian Registry of Clinical Trials (IRCT20231108059991N1). Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

## Disclosure

The authors declare that they have no conflicts of interest.

## CRediT authorship contribution statement

**Fatemeh Asadi:** Writing – original draft, Investigation, Data curation. **Elaheh Emadi:** Writing – original draft, Validation, Methodology. **Reza Chaman:** Writing – review & editing, Project administration. **Pejman Porouhan:** Writing – original draft, Investigation. **Mahboobeh Nematshahi:** Writing – original draft, Formal analysis. **Babak PeyroShabany:** Writing – original draft, Investigation. **Mohammad Salari Zare:** Writing – original draft, Investigation. **Seyed Alireza Javadinia:** Writing – review & editing, Supervision, Conceptualization.

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