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ORIGINAL ARTICLE

# Cold therapy to prevent paclitaxel-induced peripheral neuropathy

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## Abstract

**Purpose** This case-control study was designed to assess the efficacy of cryotherapy to prevent paclitaxel-induced painful peripheral neuropathy in women with breast cancer.

**Methods** Participants served as their own paired control, with randomization of the cooled glove/sock to either the dominant or the non-dominant hand/foot, worn for 15 min prior to, during, and 15 min after completion of the paclitaxel infusion. Outcome measures included the Neuropathic Pain Symptom Inventory, the Brief Pain Inventory, and quantitative sensory testing. Data were measured at each of six time points—baseline, post-treatment (approximately 2 weeks after the last paclitaxel infusion), and at the first, fifth, ninth, and final weekly paclitaxel treatments.

**Results** Of 29 randomized participants, 20 (69%) received at least one cryotherapy treatment, and 11 (38%) received all four cryotherapy treatments. Ten (34%) participants could not tolerate the cryotherapy, and six (21%) declined further participation at some point during the trial. Only seven participants (24%) were available for the final post-chemotherapy QST and questionnaires. There were no significant differences in measures of neuropathy or pain between treated and untreated hands or feet.

**Conclusions** Strategies to prevent painful peripheral neuropathy are urgently needed. In this current trial, dropout due to discomfort precluded adequate power to fully understand the potential benefits of cryotherapy. Much more research is needed to discover safe and effective preventive strategies that can be easily implemented within busy infusion centers.

**Keywords** Chemotherapy · Taxane · Paclitaxel · Peripheral neuropathy · Cold therapy

## Introduction

Paclitaxel and other taxane-based chemotherapies are first-line agents for both the adjuvant and neoadjuvant treatment of lymph node-positive breast cancer. Unfortunately, taxane-based agents are associated with significant and dose-dependent toxicities, notably painful peripheral neuropathy of the hands and feet. Although reported rates of paclitaxel-induced peripheral neuropathy (PIPN) vary widely, studies incorporating neurosensory testing cite up to 84% incidence of neuropathy after just one or two cycles and up to 97% incidence after completion of therapy [1]. Patients who receive higher doses of paclitaxel (with a typical threshold dose of about 300 mg/m$^2$) develop peripheral neuropathy earlier, and those who have pre-existing peripheral neuropathy all tend to develop more severe PIPN [2, 3]. This neuropathy leads to loss of manual dexterity of the hands and fingers along with impaired gait; these toxicities cause a significant decline in quality of life and limit the ability to perform even basic activities of daily living [4–7]. For breast cancer patients who are often relatively young at the time of diagnosis, PIPN can be so debilitating that it limits the dose of paclitaxel received [7–9] and therefore has the potential to affect survival as well as quality of life.

Because taxane-based therapies are so integral to the treatment of breast cancer, several attempts to prevent or limit taxane-induced peripheral neuropathy have been made and, unfortunately, have been unsuccessful [10]. For example, amifostine, minocycline, and recombinant human leukemia inhibitory factor had no effect in reducing peripheral neuropathy secondary to taxane therapy [11–13] and acetyl-L-carnitine significantly increased taxane-induced neuropathy in a randomized, double-blind trial [14]. A clinical practice guideline from

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the American Society of Clinical Oncology concluded that there are no agents recommended for prevention of any chemotherapy-induced peripheral neuropathy [15].

In addition to pharmacologic agents, studies have examined the use of cryotherapy to prevent the development of taxane-induced side effects. However, these studies have been limited by study design or by participant ability to tolerate the intervention. One case-control study of 45 subjects published significant success in reducing both the incidence and severity of taxane-induced skin and fingernail toxicities with the use of a frozen gel glove; these results were later replicated in two larger studies of 52 and 122 subjects [16–18]. However, the assessors of toxicities in these studies were not blinded, which may prove to be a significant limitation. A blinded case-control study ($n$ = 53) published by McCarthy et al. in 2014 evaluated the efficacy of frozen gel gloves at reducing cutaneous (skin and nail) side effects of docetaxel; however, this study ultimately lacked the power to detect such an effect due to a high participant withdrawal rate as a result of inability to tolerate the frozen glove intervention [19]. A more recent study published by Sato et al. demonstrated a significantly lower rate of PIPN in participants who wore frozen gel gloves and socks ($n$ = 182); however, this study was non-randomized and non-blinded, and the control group was selected retrospectively [20]. A small pilot trial of continuous-flow limb hypothermia to prevent PIPN suggested efficacy while being safe and tolerated by patients [21].

Given the high incidence, severity, and often permanence of peripheral neuropathy caused by taxane-based chemotherapy, this study was designed to assess the efficacy of cryotherapy to prevent PIPN in women with breast cancer. Subjects wore an Elasto-Gel™ frozen glove and sock prior to, during, and after paclitaxel infusions, and both self-reporting and quantitative sensory testing (QST) were used to determine the efficacy of this form of cryotherapy.

## Methods

### Study design

This is a randomized control study of taxane-naïve female patients receiving dose-dense anthracycline plus paclitaxel therapy for breast cancer. Data were measured at each of six time points: time point 1 (at least 2 weeks prior to the first paclitaxel infusion), time point 6 (approximately 2 weeks after the last paclitaxel infusion), and at the first (time point 2), fifth (time point 3), ninth (time point 4), and final (time point 5) weekly paclitaxel treatments.

Research questions included the following:

1. Is there a difference in "numbness" and "tingling" between treated and untreated extremities at the conclusion of paclitaxel therapy as measured by the Neuropathic Pain Symptom Inventory [22], or NPSI?
2. Is there a difference in pain intensity between treated and untreated extremities at each time point as measured by the Brief Pain Inventory [23], or BPI?
3. Is there a difference in quantitative sensory testing (QST) between treated and untreated extremities at baseline and post-treatment?

All testing was conducted by a specially trained research assistant who had been educated in quantitative sensory testing by a pain neurologist, with intermittent observation of technique for validation purposes.

### Setting, participants, and recruitment

The Robert H. Lurie Comprehensive Cancer Center at Prentice Women's Hospital is an academic teaching facility located in a large urban center. Patients were recruited either by clinician referral or by IRB-approved public postings located in outpatient clinics. Interested patients needed to meet the following inclusion criteria: females age 18 years or older with histologically confirmed breast cancer receiving adjuvant or neo-adjuvant dose-dense anthracycline (AC) plus taxane-based chemotherapy. Patients were excluded if they had received any prior taxane treatments or if they had a history of peripheral neuropathy, diabetes mellitus, or Raynaud's disease. Interested and eligible patients then underwent informed consent in clinic, ideally during their third AC treatment.

### Randomization

Participants served as their own paired control, with randomization of the intervention (Elasto-Gel™ glove/sock) to either the dominant or the non-dominant hand/foot. Participants were randomized in blocks of four, using a random number generator.

### Cryotherapy intervention

Patients wore a glycerine-containing Elasto-Gel™ glove and sock over a disposable glove and sock liner secured by Velcro at the wrist and ankle. The glove and sock were maintained at − 25 to − 30 °C in a freezer for 3 h prior to application. To maintain the appropriate cold, the study coordinator replaced the glove and sock every 45 to 50 min during the treatment. Patients wore the glove and sock for 15 min prior to and 15 min after completion of the paclitaxel infusion, as well as throughout the 180-min infusion, for a total of 210 min. If patients were unable to wear the glove

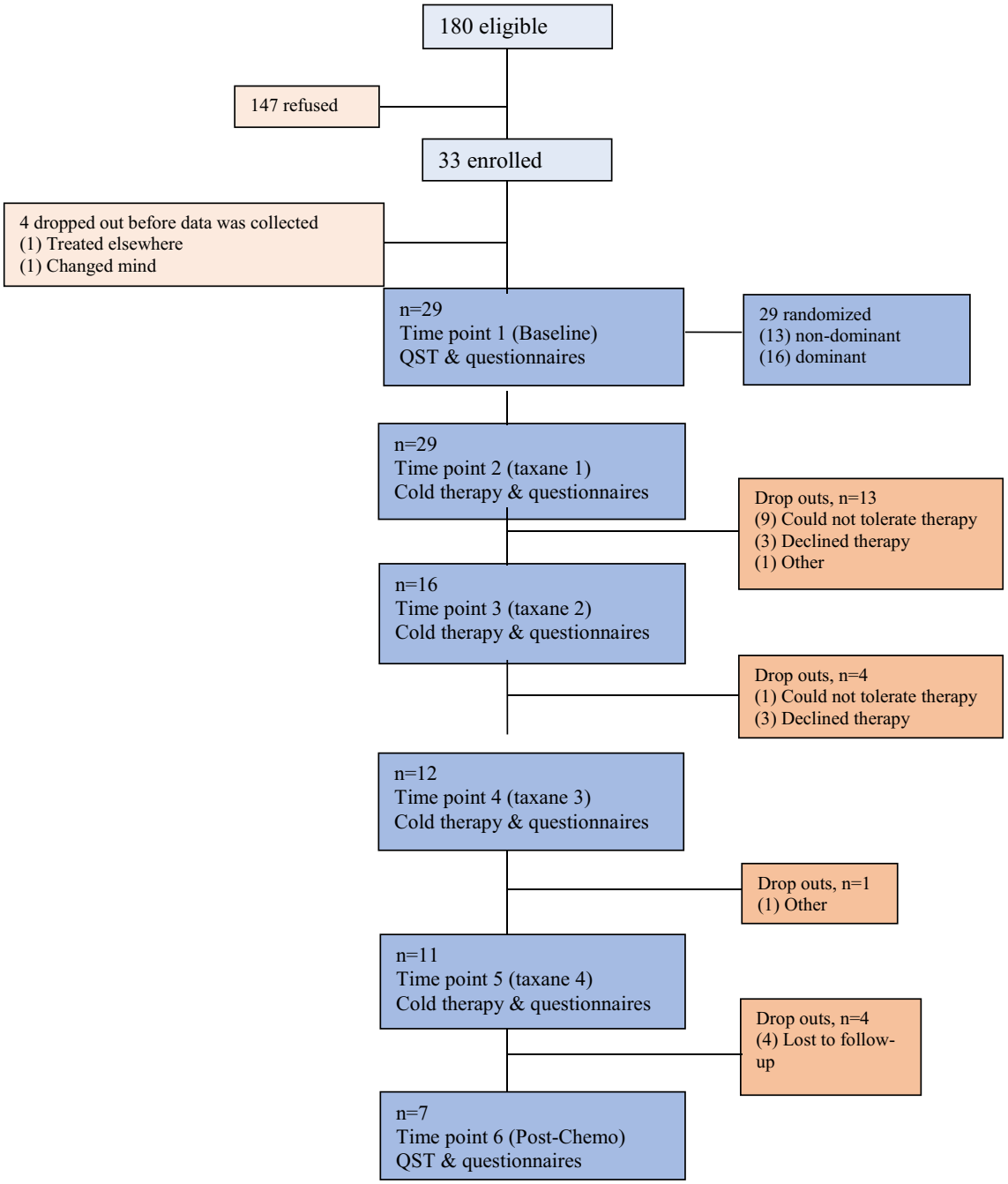



**Fig. 1** CONSORT diagram

and sock for at least the first 90 min (15 min prior to and 45 min into the infusion), then these data were considered to be incomplete; however, these patients were allowed to continue with the cold therapy at subsequent treatments.

## Outcome variables and measures

Outcomes of interest were symptoms of neuropathic pain, pain severity, and sensory sensitivity (measured with the NPSI, BPI, and QST, respectively) for the intervention versus control extremity at the end of the paclitaxel treatments. The NPSI was developed to evaluate the different symptoms of neuropathic pain, including spontaneous ongoing or paroxysmal pain, evoked pain, and dysesthesias [22]. The NPSI has 10 items using a numerical rating scale of 0 to 10 quantifying the degree to which subjects experience a variety of sensations common in neuropathy, such as "burning" and "tingling." A total score is obtained by calculating the sum of these 10

descriptors (range = 0–100). Reliability and validity have been established in a population of patients with a variety of central and peripheral neuropathies [22].

The BPI score measuring average participant worst pain, least pain, average pain, and pain at time of survey using a 0 to 10 numerical rating scale was another patient-reported outcome. The BPI has been validated in numerous populations of cancer-related pain and has been found to be feasible in studies of CIPN [23–25]. Minimally important changes for the 0–10 scales include a 10–20% change and a 1 point decrease in the interference scale [26]. And lastly, five domains of QST were measured at baseline prior to any paclitaxel exposure and 2 weeks after completion of the final paclitaxel infusion. The QST tests included the monofilament test for sensitivity to innocuous touch (which tests mechanical detection threshold using von Frey hairs which exerted mechanical forces ranging from 0.008 to 300 g), the Neuropen® test for sensitivity to noxious pinprick stimulus (calibrated to exert a force of 40 g), the Rydel-Seiffer test for sensitivity to vibratory tuning fork sensation (64 Hz), the 25-hole pegboard test for manual dexterity, and the pellet retrieval test for fine motor dexterity [27, 28]. The German Network on Neuropathic Pain protocol used to guide the application of these QST measures [28–31] has been employed in numerous trials of CIPN.

Outcome measures occurred at six time points built around paclitaxel administration, as shown in Fig. 1.

## Statistical methods

Statistical analyses and data management were performed with SPSS for Windows version 17. Paired *t* tests were used to compare scores on intervention and control extremities, and percentages were analyzed with the McNemar test. Data analyses were performed separately for each of the six time points. According to nQuery Advisor, version 5, 66 subjects were needed to generate an 80% power to detect a difference of 25% between intervention and control extremities with a significance level of 0.05. With an initial anticipated drop-out rate of 10%, a target enrollment of 74 subjects was set for this study.

## Sample

Once recruited for the study, participant characteristics including race, marital status, body mass index, and age were obtained. There were no statistically significant differences on age, race, or marital status between those who elected to enroll in the study versus those who chose not to participate. The mean dose of paclitaxel received by the randomized participants (in mg/m$^2$) was 185, 184, 183, and 173 as measured at the first, fifth, ninth, and final treatments, respectively. The mean cumulative dose of paclitaxel received by the randomized participants was 711 mg/m$^2$.

Of the 180 eligible participants who were approached to participate, 147 (82%) elected not to enroll, potentially due to competing trials occurring concurrently at our institution. Additionally, many women declined participation as they wanted to try the cryotherapy on both limbs, not just the randomized limb. Of the 33 participants who did enroll, 29 were randomized to the intervention (13 participants to the non-dominant hand, 16 patients to the dominant hand). Four either changed their minds or decided to receive treatment at another institution. The demographics of enrolled participants are summarized in Table 1.

Data were collected from all 29 randomized participants at time point 1 and time point 2; however, only 16 participants remained in the study following the fifth treatment session (time point 3). Inability to tolerate the cryotherapy was the most frequent reason that participants dropped out,

**Table 1** Participant demographics ($N = 29$)

| | | |
|---|---|---|
| Age in years (mean, range) | | 47.3 (35–68) |
| Race (*N*, %) | Black/African American | 6 (21) |
| | White | 22 (76) |
| | Hispanic/Latino | 1 (3) |
| Marital status (*N*, %) | Married | 16 (55) |
| | Single | 9 (31) |
| | Single/divorced | 4 (14) |
| Smoking status | No | 22 (88) |
| | Yes | 2 (8) |
| | Quit | 1 (4) |
| Alcoholic drinks per week (mean, range) | | 1.3 (0–7) |
| Body mass index (mean, range) | | 28.5 (17.5–44.4) |
| Treatment status | Adjuvant | 18 (62) |
| | Neoadjuvant | 11 (38) |

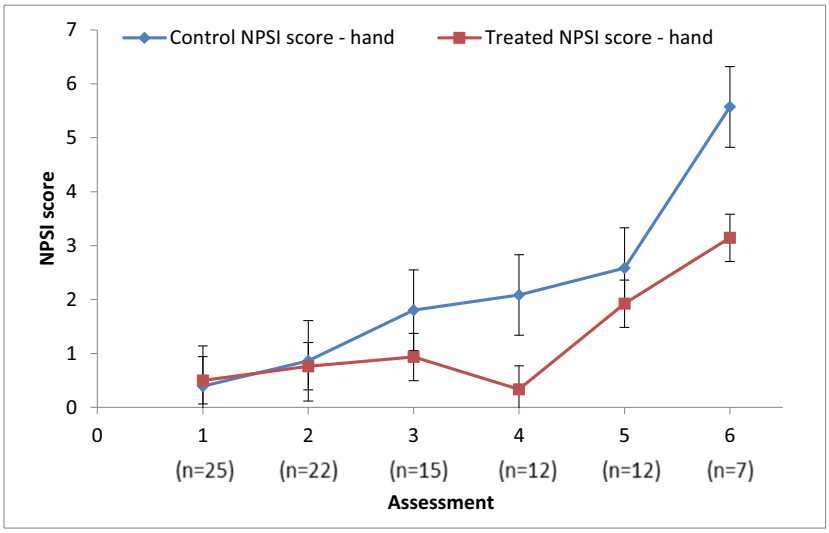
including 9 of the 13 participants who dropped out of the study after time point 2. At time point 4 (following the ninth paclitaxel treatment session), another participant dropped out because of lack of cryotherapy tolerance and three dropped out for other reasons, leaving 12 patients in the study. At time point 5 (following the final paclitaxel infusion), one patient had dropped out for reasons not related to cryotherapy tolerance and 11 participants remained in the study. At the final post-chemotherapy time point 6 data collection, only seven participants (24% of all randomized) remained and the other four participants were lost to follow-up. These results are summarized in Fig. 1.

## Results

Using a paired *t* test, there was no significant difference in NPSI scores between treated and untreated hands (all $p > 0.15$) or feet (all $p > 0.30$) (Fig. 2) at any assessment point; this remained true even when limiting analysis to the subset of seven participants who had data for the final post-chemotherapy assessment.

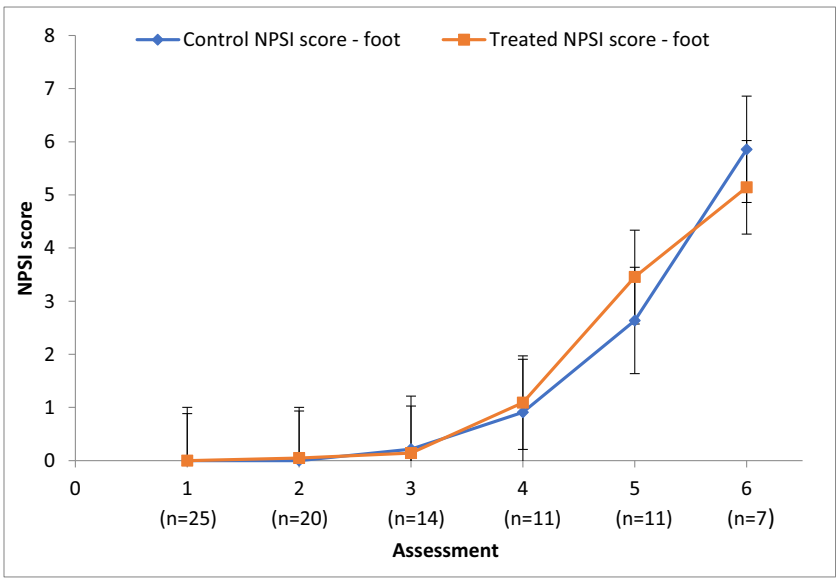
With regard to pain severity measured with the BPI, participants' ratings of pain interference (with daily physical activity, mood, relationships, sleep, and enjoyment of life), worst pain experienced in the last 24 h, average pain experienced in the last 24 h, and pain experienced at time of survey, all increased from

(a) Hands




Mean scores ± standard error of mean

(b) Feet




Mean scores ± standard error of mean

**Fig. 2** Neuropathic Pain Symptom Inventory (NPSI) scores. **a** Hands. Mean scores ± standard error of mean. **b** Feet. Mean scores ± standard error of mean

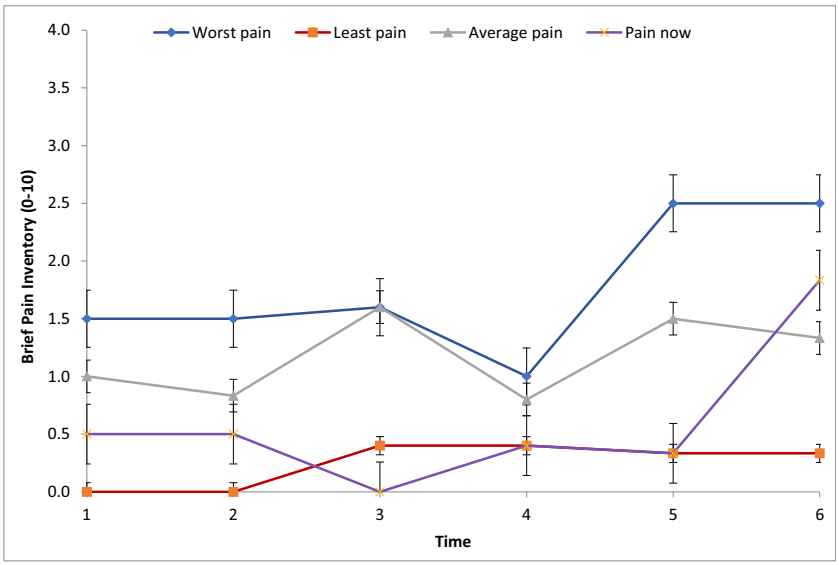



**Fig. 3** Brief Pain Inventory results. Mean scores ± standard error of mean

Mean scores ± standard error of mean

time point 1 to time point 6. Participants' least pain score experienced in the last 24 h actually decreased from time point 1 to time point 6; however, when evaluating only the subset of participants with time point 6 data, the least pain score increased as one might expect (Fig. 3) [12].

Using a paired *t* test to compare treated versus untreated hands and feet, there was no significant difference in any of the five QSTs used to measure peripheral neuropathy (all $p > 0.15$): sensitivity to innocuous touch, sensitivity to noxious stimuli, sensitivity to vibration, manual dexterity, and fine motor dexterity (Table 2).

## Discussion

This randomized, controlled trial investigating the efficacy of cryotherapy for prevention of paclitaxel-induced painful peripheral neuropathy was unable to demonstrate benefit of this non-pharmacologic technique, at least in part due to a high dropout rate among subjects due to discomfort associated with the intervention. As published in some previous studies, cryotherapy at − 25 °C applied to the hands and feet results in a significant amount of pain and discomfort [32] and leads to an increase in participant dropout rate. For example, pilot data from McCarthy et al. demonstrated a high attrition rate when using gloves cooled to − 25 °C due to inability to tolerate glove temperature without an improvement in participant tolerance even when glove temperature was increased to − 4 to − 10 °C [19]. Other studies that have explored the efficacy of cryotherapy for prevention of cutaneous toxicities associated with taxanes, such as onycholysis and skin sloughing, did not report these same rates of dropout. However, the duration of the cryotherapy intervention in these studies was typically only 60–90 min [16–18]. In another study of cryotherapy for prevention of PIPN, patients wore the cooled gloves and socks for 3 h during the chemotherapy infusion [20]. Patients receiving cryotherapy had lower incidence of grade ≥ 2 PN when compared with control group retrospective medical record PN data.

Practical issues associated with introducing new supportive therapies into the clinical setting must be considered. The

**Table 2** Quantitative sensory testing (QST) paired *t* tests of differences in control versus treated limbs at time point 6

| QST | | Difference (SD) | *p* value |
|---|---|---|---|
| Innocuous mechanical touch force (g) (monofilament test) | Hand | 0.28 (0.54) | 0.157 |
| | Foot | − 0.20 (0.47) | 0.233 |
| Noxious mechanical touch force (g) (Neuropen® test) | Hand | − 0.08 (0.45) | 0.637 |
| | Foot | 0.05 (0.46) | 0.788 |
| Vibration perception (vibration threshold) (tuning fork test) | Hand | 0.05 (0.49) | 0.807 |
| | Foot | 0.48 (1.39) | 0.397 |

present trial originated when patients were asking to use cryotherapy, yet system issues complicated its use and led the oncology team to question the risk benefit of offering this intervention. Additional freezers were installed in the clinic to adequately cool the gloves and socks; they had to be maintained and monitored regularly. Disposable liners needed to be obtained to ensure hygiene and safety. To ensure integrity of cooling, these devices needed to be changed every hour, requiring significant staff time in a very busy infusion center. Our findings were consistent with those reported by McCarthy et al. [19]. Patient discomfort was significant, leading to cessation of the trial, and logistical issues limited the use of this therapy.

There are several limitations associated with this trial that must be considered. Due to the nature of the Elasto-Gel™ glove and sock, the participants could not be blinded to the intervention, which may affect responses to both the self-reported NPSI and BPI questionnaires as well as reporting for the NCI-CTC v4.0. The QSTs were administered by trained researchers, and techniques for collection of these data were confirmed by a neurologist specializing in pain research. The research assistant who applied the gloves and socks also performed the QST, potentially introducing bias.

Additionally, the study is limited by the small sample size. Despite recruiting 180 subjects for a target of only 74 participants, less than half of this target number was achieved for randomization. This may suggest that the extra time required for both the intervention as well as the data collection posed too great a commitment for patients. Of the 29 subjects who did agree to enrollment and randomization, there was a subsequent high dropout rate, further limiting this study. When it became clear that subjects could not tolerate the 210-min duration of therapy, the study was stopped. At the time of study discontinuation, only seven patients (4% of the original recruited population) had tolerated all four cryotherapy treatments and were available for data collection. This extremely low number of remaining patients calls into question the feasibility of both the cryotherapy intervention and the extensive data collection required of each participant.

One potential strategy to decrease dropout rate due to patient discomfort would be to decrease the time the participant is required to wear the Elasto-Gel™ glove and sock; for example, patients may still receive some benefit from receiving cryotherapy for just the first 60 min of a taxane infusion. The feasibility of future studies could be further increased by performing data collection in different phases. For example, in the first phase, only subjective data (e.g., NPSI and BPI scores) would be collected and reported, and in subsequent phases, the objective QSTs could be performed. Limiting the time and energy commitment from subjects who are already likely very fatigued from their cancer and treatment may improve enrollment rates.

Chemotherapy-induced peripheral neuropathy remains a serious consequence of cancer therapy impairing quality of life and potentially leading to inadequate doses of potentially curative treatment. Strategies to prevent painful peripheral neuropathy are urgently needed. In this current trial, dropout due to discomfort associated with the intervention and potentially feasibility limitations of the study itself precluded adequate power to fully understand the potential benefits of cryotherapy. Much more research is needed to discover safe and effective preventive strategies that can be easily studied and implemented within busy infusion centers.

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## Compliance with ethical standards

**Conflict of interest** Southwest Technologies provided the devices used in this clinical trial. None of the authors has a financial relationship with this organization or other conflicts of interest. Southwest Technologies did not have access to the data nor were they involved in authorship of this paper. The corresponding author has full control of the primary data and agrees to allow the journal to review the data on request.

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