

## Original article

# Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial



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## ABSTRACT

**Background:** Recently, the efficacy of cryotherapy and compression therapy to prevent taxane-induced peripheral neuropathy has been reported. We prospectively compared the efficacy of cryotherapy using a frozen glove (FG) and compression therapy using a surgical glove (SG) to prevent nanoparticle albumin-bound paclitaxel (nab-PTX)-induced peripheral neuropathy.

**Patients and methods:** Breast cancer patients who received 260 mg/m<sup>2</sup> of nab-PTX were eligible to participate in this trial. Patients wore a FG on one hand (60 min) without changing and two SGs of the same size (i.e., one size smaller than the size that best fit their hand) on the other hand (90 min) during chemotherapy. Peripheral neuropathy was evaluated at each treatment cycle using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, the Patient Neurotoxicity Questionnaire (PNQ), and the Functional Assessment of Cancer Therapy-Taxane subscale. Temperatures at each fingertip in both groups were measured thermographically.

**Results:** Between August 2017 and March 2019, 43 patients were enrolled and 38 were evaluated. No cases showed discordance of peripheral neuropathy between each gloved group in cases of CTCAE  $\geq$  grade 2. In cases of PNQ  $\geq$  grade D, using the Nam equivalence test, the upper test ( $P = 0.0329$ ) and lower test ( $P = 0.0052$ ) both showed negative results in comparisons between each gloved group. Fingertip temperature was significantly lower in the FG group than in the SG group after treatment ( $P < 0.0001$ ). **Conclusions:** It seems to be no difference in incidence of nab-PTX-induced peripheral neuropathy using either cryotherapy or compression therapy.

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## 1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) accompanies the administration of drugs such as taxanes, platinum-based drugs, vinca alkaloids, resulting in a major drug-induced adverse reaction that becomes a dose-limiting toxicity of chemotherapy [1,2]. CIPN reduces health-related quality of life [3,4] and often

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results in dose delay, dose reduction, or treatment discontinuation [5]. Taxanes are among the key cytotoxic anticancer agents for primary and metastatic breast cancer treatment. As a solvent-free formulation of paclitaxel (PTX), nanoparticle albumin-bound PTX (nab-PTX) can avoid hypersensitivity reactions, and it can be administered at higher doses of PTX to the target tumor. However, nab-PTX has non-hematological toxicities, including peripheral neuropathy and acute arthralgia or myalgia (taxane acute pain syndrome) [6,7]. Previous studies have clarified that nab-PTX is associated with an increased risk of developing peripheral neuropathy [8–10]. According to the 2014 American Society of Clinical Oncology guidelines, strong evidence for the prevention and treatment of CIPN is not available [11].

In recent years, the efficacy of cryotherapy using a frozen glove (FG) [12–14] and compression therapy using surgical gloves (SGs) [15–17] to prevent taxane-induced peripheral neuropathy has been reported. SG compression therapy is an easy procedure, inexpensive compared to FG cryotherapy. However, no reports appear to have compared the efficacy of cryotherapy and compression therapy. If we can confirm equivalent efficacy of cryotherapy and compression therapy, the use of simple, inexpensive SG may be able to prevent taxane-induced peripheral neuropathy, so the potential clinical impact is extremely high. We therefore planned the present prospective, self-controlled trial to compare the efficacy of cryotherapy using FG (FG cryotherapy) and compression therapy using SG (SG compression therapy) to prevent nab-PTX-induced peripheral neuropathy.

## 2. Methods

### 2.1. Study design

In this phase II, self-controlled clinical trial, we evaluated the preventive effects of FG cryotherapy and SG compression therapy for nab-PTX-induced peripheral neuropathy. In addition, we conducted a comparative trial of the efficacies of cryotherapy and compression therapy. Women with pathologically confirmed breast cancer were eligible for this trial. Inclusion criteria were age  $\geq$  20 years, provision of signed informed consent, and ability to answer Japanese questionnaires without assistance. If no difference was seen in the degree of peripheral neuropathy between left and right hands, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade 1 was considered acceptable. Exclusion criteria were as follows: peripheral sensory/motor neuropathy (CTCAE grade  $\geq$  2), underlying diseases that could potentially cause peripheral neuropathy (such as diabetes mellitus or postherpetic neuralgia), allergy to the material of FGs (polyurethane and nylon) or the material of SGs (latex), brain metastases, or any other reasons based on the judgment of the primary physician.

This trial was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine, in accordance with the tenets of the Declaration of Helsinki (approval no. ERB-C-906-1) and was registered with the University Hospital Medical Information Network in December 2017 (UMIN000030536). Written informed consent was obtained from all patients prior to their enrollment.

Patients enrolled in this trial were undergoing treatment with 260 mg/m<sup>2</sup> of nab-PTX as 30-min intravenous infusion every 3 weeks for four cycles. Human epidermal growth factor receptor 2 (HER2)-positive patients received trastuzumab after administration of nab-PTX during each cycle.

During chemotherapy, patients wore a FG on one hand and two SGs of the same size (i.e., one size smaller than the size that best fit the hand) on the other hand continuously. Gloves were worn as follows: FG from 15 min before starting nab-PTX administration

until 15 min after the end of infusion (60 min) without changing; and SGs from 30 min before starting nab-PTX administration until 30 min after the end of infusion (90 min), following previous studies [12,15,16]. The hand wearing each glove was randomly assigned, using “dominant hand” as the allocation factor. Each subject wore gloves the same way throughout the trial period. The FG used was a frozen flexible glove, as either ELASTO-GEL (Southwest Technologies, North Kansas City, MO, USA) or Cool Mitten (Nippo Corporation, Osaka, Japan). The SGs used were widely used in daily clinical practice (Medline Industries Japan, Tokyo, Japan). The size of SG was confirmed by asking the patient to wear the SGs. After the most suitable size of SG was determined, the SG that was one size smaller was selected for use in the study.

### 2.2. Outcome

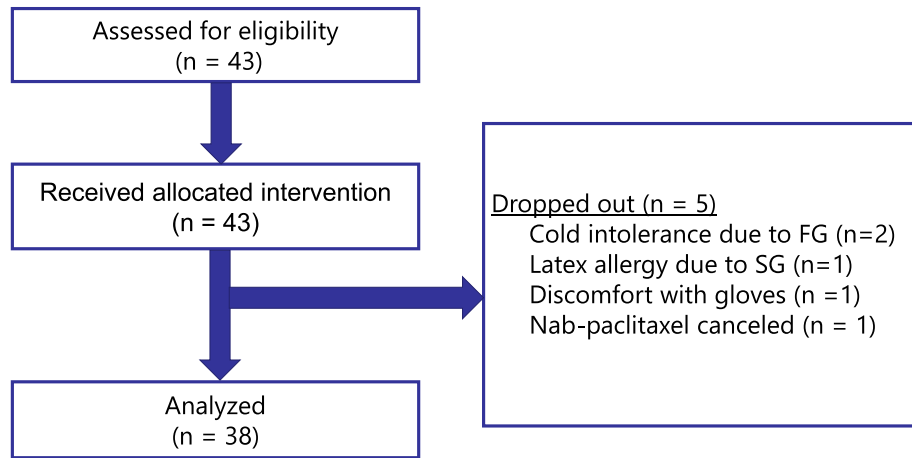
The primary endpoint was to compare frequencies of CTCAE version 4 grade  $\geq$  2 and Patient Neurotoxicity Questionnaire (PNQ) grade  $\geq$  D (neuropathy interfering with activities of daily living [ADL]) peripheral neuropathies [18] at the last evaluation between the FG-protected hand and the SG-protected hand. Secondary endpoints were to compare changes during every cycle of nab-PTX-induced peripheral neuropathy using the PNQ and the Functional Assessment of Cancer Therapy-Taxane (FACT-T [19], and to compare changes in temperatures at the tip of each finger using thermography.

### 2.3. Evaluation of peripheral neuropathy

Peripheral neuropathy was evaluated by treating pharmacists and/or nurses using National Cancer Institute CTCAE version 4.0 at the following times: pretreatment (baseline); just before each treatment cycle; and six weeks after chemotherapy completion ( $\pm$ 2 weeks). Peripheral neuropathy was also evaluated using the Japanese version of the PNQ, a validated patient-reported questionnaire on neuropathy and ADL that correlates with quality of life [18], and 4 items related to neurological disorders excerpted from FACT-T [19]. The PNQ comprises two items (sensory and motor neuropathy). The subjective responses to each item are graded from A to E by the patient. Each item of PNQ was defined as A (no neuropathy), B (mild neuropathy), C (moderate neuropathy that does not interfere with ADL), D (moderate neuropathy that interferes with ADL), or E (severe neuropathy that interferes with ADL). There is specific demarcation between grades C and D corresponding to the absence (grade  $\leq$  C) and presence of symptoms (grade  $\geq$  D) that interfere with activities of daily living [18]. In this trial, PNQ grades were coded as 1–5, with higher score indicating more severe peripheral neuropathy. On the other hand, the four items extracted from FACT-T related to neurological disorders in hands were: 1) “I have numbness or tingling in my hands”; 2) “I have trouble buttoning buttons”; 3) “I have trouble feeling the shape of small objects when they are in my hand”; and 4) “I have pain in my fingertips”. FACT-T is evaluated using a 5-point scale: 0 indicates not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much, giving a total score range for the four items of 0–16.

### 2.4. Evaluation of fingertip temperatures

To investigate mechanisms underlying protection against peripheral neuropathy, the temperature at each fingertip was measured by thermography at the first cycle of nab-PTX. Temperatures at each fingertip on both hands were measured before wearing gloves and 30 min after the end of nab-PTX infusion using a thermographic camera (INFRA-EYE 2000; Fujitsu, Tokyo, Japan). For SGs, the top of the SG of each finger was cut by scissors, and



**Fig. 1.** Of the 43 patients enrolled, 38 patients were evaluated in this trial. Five patients withdrew from the trial and thus were excluded from analysis, due to intolerance of cooling from the FG (n = 2), onset of latex allergy due to SG (n = 1), discomfort with gloves (n = 1), and cancellation of nab-PTX after second cycle (n = 1).

each fingertip was measured by thermography.

### 2.5. Statistical analysis

The incidence of Grade  $\geq 2$  CIPN in nab-PTX therapy is reportedly around 50% [20–22]. Examination of past cases in our hospital showed a similar incidence of 50%. From previous reports, we anticipated an incidence of 20% when wearing the FG or SGs. The required number of cases for which the 90% confidence interval of the difference of this ratio falls within 25% (equity margin) is 30 cases with  $1-\beta = 0.8$ . The incidence of peripheral neuropathy of Grade  $\geq 2$  with nab-PTX therapy was 50%, so we set the equality margin as 25% below the 30% difference with the expected incidence of 20% in this test group (FG or SG group). We therefore planned to register 34 cases in anticipation of some dropout cases.

The significance level of the test is 10% on both sides. As an equivalence comparison between the efficacy of cryotherapy and compression therapy for CIPN (as the primary endpoint), the Nam equivalence test [23] (an extension of McNamar's test) was performed for equivalence comparisons. A one-sided test (upper and lower) was used to determine whether the difference in proportion between the two groups was within the equality margin.

In the comparison of secondary endpoints (CIPN and temperatures at the fingertips) between both groups, the Wilcoxon matched-pairs rank test was used to determine the degree of difference in the grade of neuropathy and temperature at the fingertip. For both PNQ and FACT-T evaluations, two-way repeated-measures analysis of variance was used to compare temporal differences in the occurrence of CIPN between the two groups. For all statistical analyses, values of  $P < 0.05$  (2-tailed) were considered significant. All analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) and JMP version 14.3.0 (SAS Institute, Cary, NC), supervised by a statistician.

## 3. Results

### 3.1. Patient recruitment and characteristics

Between August 2017 and March 2019, a total of 43 patients with breast cancer were enrolled. In this clinical study, 34 patients were planned anticipating some drop out. However, there were many dropout cases at an early stage. We thought that there were more dropouts than expected. So, total of 43 patients were enrolled. Of those, 38 patients were evaluated in this trial (Fig. 1; Table 1).

Five patients withdrew from the trial. Reasons for withdrawal included an inability to tolerate cooling by the FG (n = 2), onset of latex allergy due to SGs, discomfort with gloves, and cancellation of nab-PTX after the second cycle (n = 1 each). Median glove size was 6.0 (range, 5.5–6.5).

### 3.2. Occurrence of CIPN

The 38 patients who received nab-PTX in combination with SG compression therapy and FG cryotherapy were evaluated for CIPN. Frequencies of CTCAE grade  $\geq 2$  and PNQ grade  $\geq D$  peripheral neuropathies at last evaluation are shown in Table 2a-b. In both FG

**Table 1**  
Patient characteristics (n = 38).

Demographics	
Mean age (SD), years	57.6 (11.0)
Mean weight (SD), kg	53.8 (9.8)
Mean body mass index (SD), kg/m <sup>2</sup>	21.8 (3.9)
Smoking	
Smoker	0
Smoking history, n (%)	11 (28.9)
ECOG performance status	
0, n (%)	36 (94.7)
1, n (%)	2 (5.3)
Left-handed, n (%)	1 (2.6)
Dominant hand that wore the FG glove, n (%)	20 (52.6)
Glove size, n (%)	
5.5, n (%)	18 (47.4)
6.0, n (%)	15 (39.5)
6.5, n (%)	5 (13.2)
Breast cancer	
Left, n (%)	16 (42.1)
Right, n (%)	22 (57.9)
Treatment	
Neo-adjuvant, n (%)	25 (65.8)
Adjuvant, n (%)	11 (28.9)
Palliative, n (%)	2 (5.3)
Combination therapy with trastuzumab, n (%)	16 (42.1)
Cumulative dose of nab-PTX, median (range), mg	1040 (920–1040)
Subtype of primary tumor	
ER + HER2-, n (%)	13 (34.2)
ER + HER2+, n (%)	9 (23.7)
ER-HER2+, n (%)	4 (10.5)
ER-HER2-, n (%)	12 (31.6)

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; FG, frozen glove; nab-PTX, nanoparticle albumin-bound paclitaxel; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

**Table 2a**  
Classification of patients evaluated by CTCAE.

	SG group (CTCAE ≥ Grade 2)	SG group (CTCAE < Grade 2)
(a) Peripheral sensory neurotoxicity (n = 38)		
FG group (CTCAE ≥ Grade 2)	7	0
FG group (CTCAE < Grade 2)	0	31
(b) Peripheral motor neuropathy (n = 38)		
FG group (CTCAE ≥ Grade 2)	7	0
FG group (CTCAE < Grade 2)	0	31

**Table 2b**  
Classification of patients evaluated by PNQ score

	SG group (PNQ ≥ D)	SG group (PNQ < D)
(a) Peripheral sensory neurotoxicity (n = 38)		
FG group (PNQ ≥ D)	1	1
FG group (PNQ < D)	0	36
(b) Peripheral motor neuropathy (n = 38)		
FG group (PNQ ≥ D)	1	1
FG group (PNQ < D)	0	36

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SG, surgical glove; FG, frozen glove; PNQ, Patient Neurotoxicity Questionnaire.

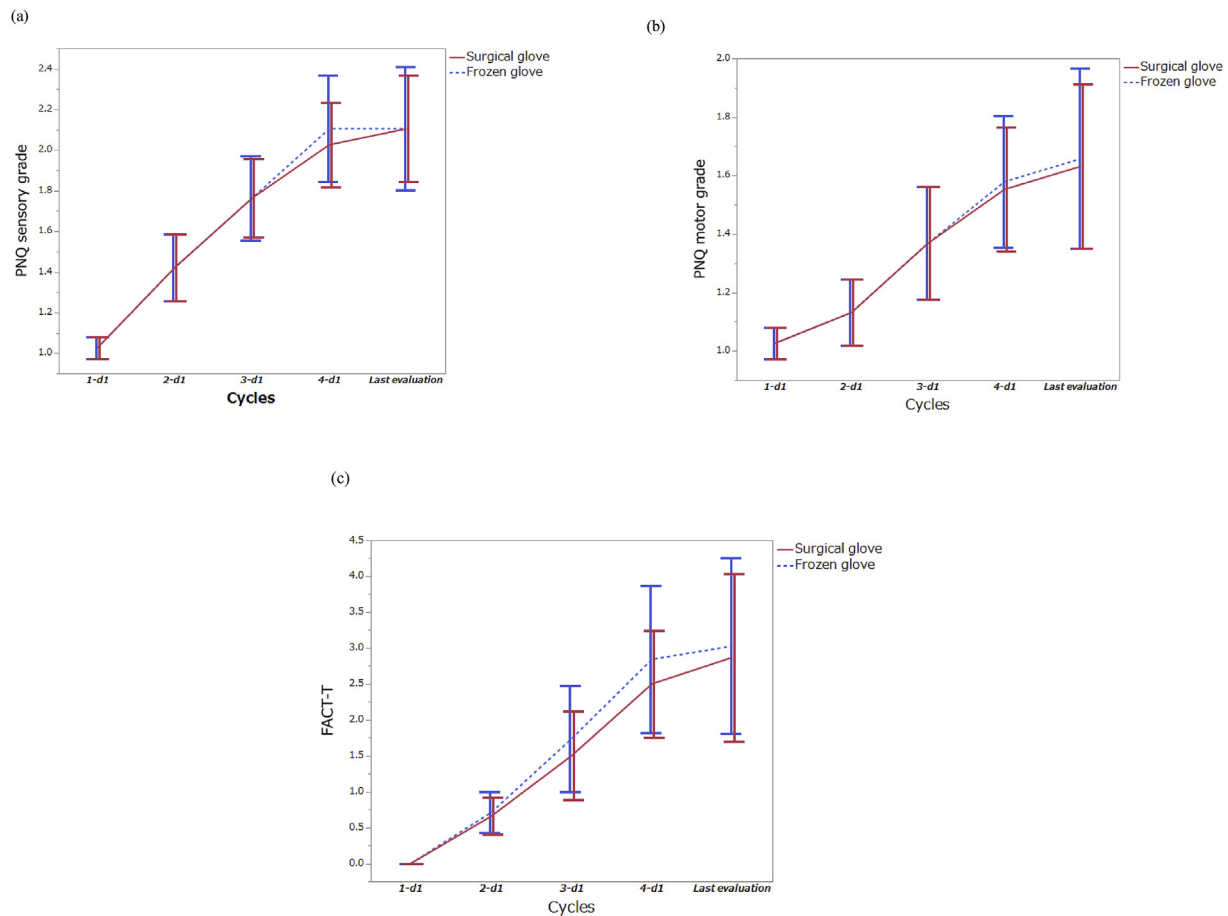
and SG groups, frequencies of CTCAE grade ≥2 was 18.4%. No patients showed discordance of peripheral neuropathy between FG and SG groups in the evaluation using CTCAE (frequency 18.4% each). In evaluating PNQ responses, upper test ( $P = 0.0329$ ) and

lower test ( $P = 0.0052$ ) for the Nam equivalence test both yielded negative results.

PNQ sensory and motor grades, and FACT-T (total grade for each of the 4 items) are shown in Fig. 2 for the scheduled times during nab-PTX treatment. No difference was identified between FG and SG groups in PNQ sensory neuropathy ( $P = 0.32-1.0$ ), PNQ motor neuropathy ( $P = 0.51-1.0$ ), or total FACT-T score ( $P = 0.67-0.93$ ) at each evaluation time. During administration of nab-PTX, 20 patients (52.6%) were permitted to take additional medications such as vitamin B12, goshajinkigan, pregabalin, duloxetine, and/or tramadol because peripheral neuropathy grade ≥2 affected their feet.

### 3.3. Changes in fingertip temperature

We investigated the mechanism of how SG compression therapy or FG cryotherapy reduces the incidence of nab-PTX-induced



**Fig. 2.** Temporal comparison of grades of peripheral neuropathy using PNQ sensory and motor grades, and FACT-T between cooling FG-protected hands (n = 38) and compression SG-protected hands (n = 38) during nab-PTX treatment. No grades of peripheral neuropathy over the course of four cycles of treatment showed any significant differences between cooling FG-protected hands and compression SG-protected hands. Error bars represent 95% confidence interval.

peripheral neuropathy. Thermography was used to measure the temperature at each fingertip of both hands after chemotherapy in 19 patients. Use of the FG significantly decreased mean temperature at each fingertip by 8.3–9.8 °C, as compared with measured value before wearing FGs ( $P < 0.0001$ ). Similarly, use of SGs significantly decreased mean fingertip temperature by 3.0–3.8 °C ( $P < 0.0001$ ) (Fig. 2). Mean fingertip temperature showed no significant difference between groups before treatment (FG, 31.3 °C vs. SG, 31.3 °C), but was significantly cooler in the FG group (22.3 °C) than in the SG group (27.9 °C;  $P < 0.0001$ ) in all fingertips after treatment (Fig. 3).

#### 3.4. Adverse Events associated with FG cryotherapy or SG compression therapy

Two patients withdrew from the trial because they could not tolerate cooling using FG. On the other hand, one developed latex allergy due to SG. After discontinuation, allergic symptoms improved. Questionnaires given to patients prior to this trial did not indicate presence of latex allergy in any patients. Although 38 patients completed their four cycles of nab-PTX, two patients required dose reductions of nab-PTX due to CIPN or taxane acute pain syndrome that developed involving the feet.

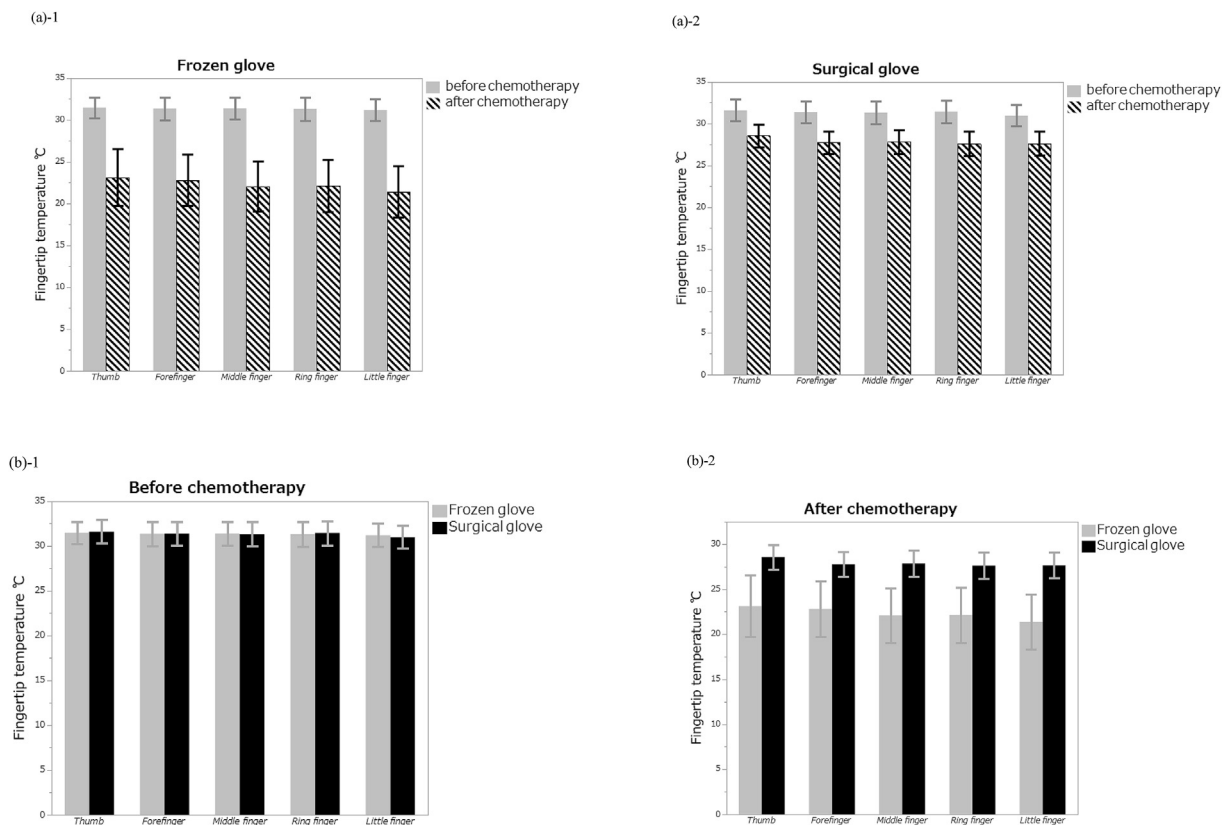
## 4. Discussion

The incidence of CIPN in FG- or SG-protected hands was similar to previous studies [12,15,16] in both CTCAE and PNQ evaluations, so it appeared that the utility of FGs or SGs in preventing peripheral neuropathy was similar in this trial. Furthermore, we demonstrated cryotherapy and compression therapy seemed to offer similar

efficacy in preventing nab-PTX-induced peripheral neuropathy for the first time in a prospective investigation.

SG compression therapy is an inexpensive, feasible method to prevent peripheral neuropathy. SG compression therapy is an easy procedure, with a low cost of only 280 Japanese yen (JPY) per pair of gloves. In this trial, we clarified that the use of inexpensive and simple SGs can prevent the development of nab-PTX-induced peripheral neuropathy. Unfortunately, one patient dropped out of this trial due to latex allergy. On the other hand, FGs are usually dried overnight after use and then frozen overnight or more. FGs are quite expensive, at 18,000 to 28,000 JPY per pair of gloves. A special freezer maintained at  $-25$  °C to  $-30$  °C is also needed to prepare the FGs. In previous trials, several percent of patients dropped out after experiencing discomfort due to cold intolerance [13,24]. In our trial, two patients withdrew because they could not tolerate the cooling using FG. Although both glove types have drawbacks, the equivalence of the prophylactic effects against CIPN was clarified. More preventive options are thus available for patients, and our results should greatly contribute to the improvement of QOL in patients undergoing taxane-based chemotherapy.

Hanai et al. discussed how compression therapy and cryotherapy share an analogous mechanism of reducing drug exposure due to vasoconstriction during paclitaxel infusion [12]. The low temperature associated with cryotherapy may also decrease the uptake of paclitaxel and damage to neurons or mechanotransductions, which might be related to decreased CIPN. The temperature at each fingertip decreased significantly after chemotherapy. However, temperature in the FG-protected hand was significantly lower than that in the SG-protected hand. A comparable extent of blood flow reduction can thus be obtained by both SG compression therapy and FG cryotherapy. The influence of



**Fig. 3.** Changes in temperature at each fingertip subjected to FG cryotherapy or SG compression therapy ( $n = 19$ ). After chemotherapy, both SG compression therapy and FG cryotherapy hands significantly decreased the temperature at each fingertip, as compared with measurements taken before wearing the gloves. Fingertip temperature showed no significant difference between groups before treatment, but was significantly lower in the FG group than in the SG group after treatment for all fingertips.

lower uptake of anticancer drugs to fingers may be not only vasoconstriction due to low temperature but also compression. If we could exclude patients with latex allergy in advance, SG would carry no risk of frostbite and would be an easy and safe option for preventing CIPN.

However, some patients still develop CIPN (CTCAE  $\geq$  Grade 3 or PNQ  $\geq$  D) even after taking such preventive measures. Risk factors for CIPN such as genetic polymorphism have already been reported [25,26], but the interrelationship of CIPN and genetic polymorphism in particular needs to be verified at a later date. Further investigation of these issues is needed.

Our trial had several limitations that warrant consideration. First, no control cases were included. Second, we evaluated CIPN using CTCAE, PNQ, and FACT-T, all of which are subjective methods. Other examinations might be needed to provide objective evaluation of CIPN (i.e., nerve conduction velocity [NCV] methods, thermosensory disturbance, vibration perception, and performance speed) [12]. Third, since we conducted no intervention on feet, the placebo effect cannot be denied. Fourth, use of FG was suboptimal since around the time of peak concentration of chemotherapy, FGs were not as cold as pivotal study. Fifth, this trial permitted the use of preventive or therapeutic agents for CIPN. The effects of drugs cannot be denied. However, as strong evidence for the prevention and treatment of CIPN is not available for any medications [1–5,11,27,28], the effects might be minimal.

We found that both FG cryotherapy and SG compression therapy appeared to be effective in preventing nab-PTX induced peripheral neuropathy. The present trial is the first prospective study to show that FG cryotherapy and SG compression therapy have comparable effects in preventing nab-PTX-induced peripheral neuropathy. The results revealing that the preventive effects of cheap, readily available SGs are equivalent to those with the FG are likely to greatly contribute to improved QOL for patients undergoing taxane chemotherapy.

## Funding

None.

## Declaration of competing interest

Isao Yokota has received a speaker's fee from Chugai Pharmaceutical Co., Ltd. Norito Katoh has been a speaker and investigator for Taiho Pharmaceutical Co., Ltd. Tetsuya Taguchi received a speaker's fee and research funds from Taiho Pharmaceutical, and Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no conflicts of interest concerning this work.

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