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Novel Frostbite Cooling Device for Real-time Assessment and Prevention of Chemotherapy-induced Peripheral Neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) affects 29%–68% of patients undergoing anticancer treatments within the first month. Traditional cryotherapy methods, such as frozen gloves, can pose risks. This study evaluates the cool-water electric circulation seat (CECS), which maintains a constant 15°C, as a safer alternative.
Methods: In this prospective study, 21 healthy Japanese adults underwent 2.5 hours of hand cooling at 15°C, reflecting the standard duration of taxane anticancer drug administration. Microcirculation was evaluated using videocapillaroscopy before and after cooling.
Results: Results showed significant reductions in blood vessel area and altered red blood cell movement postcooling. Finger temperature and vascular area decreased significantly ($P < 0.001$), and red blood cell movement changed significantly, with most cells shifting from slow (52.4%) or fast (47.6%) movement before cooling to slow (23.8%) or immobile (76.2%) afterward ($P < 0.001$). Thirty minutes postcooling, 38.1% of participants reported temporary redness, and 28.6% reported pain, both resolving by the next day.
Conclusions: The CECS effectively provides secure cooling, offering a promising approach for CIPN prevention without frostbite risk. These findings highlight the potential advantages of CECS in sustained cooling therapy for CIPN prevention.
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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a significant challenge associated with particular chemotherapeutic agents, with platinum-based drugs and taxanes being notable contributors.[1,2] Incidence rates, ranging from 29% to 68%, vary based on assessment time points, administered neurotoxic drugs, and other factors.[2–4] Nerve injury mechanisms vary, but the prevailing sensory damage manifests as pain, burning, numbness, and proprioception deficits, predominantly affecting the hands and feet in a stocking-and-glove distribution pattern.[5] The impact of CIPN extends to diminished quality of life, reduced functional abilities, potential work limitations, and an elevated risk of falls.[6–9] Symptoms contribute to depression and loss of purpose, limiting patients' once-enjoyed activities.[8] The duration of CIPN symptoms may persist for months to years post-treatment, becoming permanent in some cases.[6] The impact of CIPN extends to treatment efficacy, potentially resulting in reduced chemotherapy dosing, discontinuation of causative agents, and treatment delays.[5,10] Dose reductions due to CIPN affect 10%–24.5% of patients with breast cancer undergoing taxane therapy, with a

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higher prevalence among African American patients and those with diabetes.[5] Preventive interventions for CIPN are lacking, and treatment options have varying recommendation levels.[11,12] Recent studies explore the potential benefits of peripheral cooling, or cryotherapy, as a preventative measure for CIPN. The concept revolves around the protective effect of cooling, reducing drug distribution through vasoconstriction, and decreasing cellular uptake and biochemical activity in target tissues.[13–15] A study of 1725 patients suggested that cryotherapy with frozen gloves at −20° to −30°C prevents CIPN effectively but can lead to frostbite, resulting in a global recall of cooling equipment. Since then, the effectiveness and safety of cooling temperatures for CIPN prevention remain unknown.[16] Postexercise muscle cooling therapy with phase change material at 15°C for 6 hours has demonstrated safety without frostbite.[17] We determined whether cooling at 15°C can safely reduce peripheral blood flow using healthy volunteers. Through this integrated approach, our study aimed to provide comprehensive knowledge of CIPN prevention and work toward developing a safer and more effective cooling therapy.

Takeaways

Question: How can chemotherapy-induced peripheral neuropathy be prevented without the risks of traditional cryotherapy (around −20°C)?

Findings: The cool water electric circulation seat (CECS) maintained a safe 15°C, significantly reducing finger temperature and vascular area, and altering red blood cell movement. Most participants showed a shift from slow or fast to slow or immobile movement, indicating CECS's impact on microcirculation. Some reported temporary redness and pain, which resolved within 24 hours.

Meaning: CECS offers a safe, effective alternative for preventing chemotherapy-induced peripheral neuropathy while minimizing frostbite risk, with changes in microcirculation supporting its benefits for sustained cooling therapy.

METHODS

Study Approval and Ethical Considerations

This study was approved by the institutional review board of the Hitachi Medical Center (institutional review board: 2021H01) and conducted according to the principles of the Declaration of Helsinki.

Participant Selection and Study Design

This prospective study was conducted on 21 healthy Japanese volunteers (9 men and 12 women). The study involved sustained cooling of the left hand at 15°C for 2.5 hours, comprising 30 minutes before the simulated administration of taxane-based chemotherapy, 1 hour corresponding to the standard administration time, and 60 minutes after the administration. Because the alpha phase half-life ($t_{1/2}$ alpha) and beta phase half-life ($t_{1/2}$ beta) of docetaxel are 7.1 and 47.8 minutes, respectively, during hepatic dysfunction, the cooling time after administration was 60 minutes.[18]

Cooling Intervention Procedure, Videocapillaroscopy, and Data Collection

For cooling, a continuous electric circulation sheet (CECS) developed by Thermic Techno Co., Ltd., maintaining a temperature of 15°C, was utilized (Fig. 1). The CECS is a circulating cooling system with a working range from 15° to 41°C in 1°C increments. Approximately 200 mL of circulating water was injected and distributed evenly on the patented sheet. The cooled sheet was wrapped around the left hand to allow peripheral cooling. The sheet, measuring a mere 4 mm in thickness and weighing only 640 g, and the entire instrument, weighing only 1700 g, are easily portable and possess outstanding quietness owing to the absence of a compressor, which minimizes noise stress during the cooling process. In addition, the cost of this device is low at $268.90 per unit. Before and after the cooling intervention using CECS, dynamic changes in blood flow within the capillaries of the dorsum of the hand and the nail bed of the ring finger were systematically observed using videocapillaroscopy (GOKO Bscan-ZD model no. EV-80ZD; GOKO Imaging Devices Co., Ltd., Kawasaki, Japan) (Fig. 2). The data collection process involved accurate recording at 3-minute intervals before and after the cooling intervention. Subsequently, static images extracted from the videocapillaroscopy recordings were analyzed using ImageJ software. The pixel-occupied vascular area was divided by the entire view area to quantify the percentage decrease in capillary area. The capillary area reduction percentage (%) was evaluated using the ImageJ software, following the methodology established in previous studies.[19,20] Red blood cell (RBC) movement

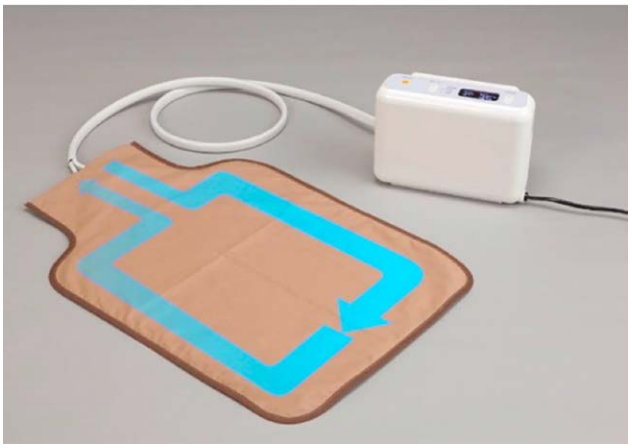

Fig. 1. The CECS boasts a very slender profile, measuring only 4 mm of thickness, and features lightweight construction, tipping the scales at 640 g. This state-of-the-art seat incorporates an innovative water circulation system. The temperature control span ranges from 15° to 41°C, with the ongoing water circulation guaranteeing steadfast temperature management. Notably, the overall device weight was 1700 g, confirming its exceptional portability.

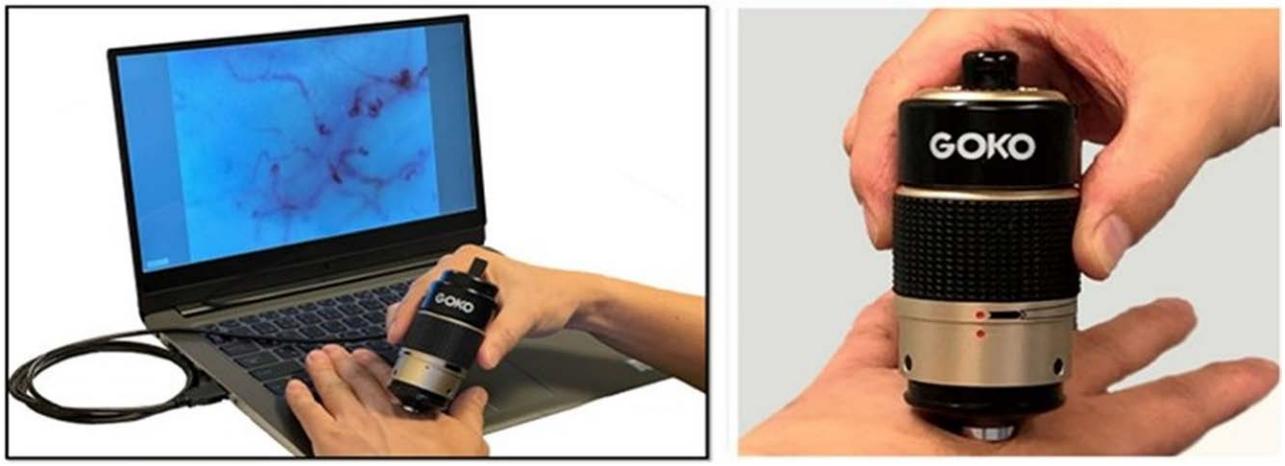

Fig. 2. The GOKO Bscan-ZD videocapillaroscope served as the apparatus for observing capillaries in the skin flap. The camera field covered 0.35 mm^2/point, reaching a depth of 1mm from the surface. Remarkably lightweight at 140 g, it allowed for effortless single-handed operation. The observations were conducted at approximately 175× and 620× magnification, boasting a resolution of 1.2 million pixels.

Fig. 3. Cooling was executed, utilizing docetaxel administration as the conceptual framework, encompassing a total cooling duration of 2.5 hours. This cooling protocol comprised a 30-minute predose cooling phase, simultaneous cooling throughout the entire period of docetaxel administration (1 h), and postadministration cooling lasting approximately 1 hours. The primary objective of this investigation was to assess the impact of the cooling regimen on the half-life ($t_1/_2$) of docetaxel.

was measured on a scale, assigning 0 points for imperceptible movement, 1 point for slow movement, and 2 points for rapid movement.

Statistical Analysis

This study compared vessel characteristics and rheological parameters using a paired *t* test. One-way analysis of variance and Tukey honest significant difference test were used to assess significant differences in the reduction rates of blood vessel area and blood flow velocity across different anatomical zones. JMP 17 software (SAS Institute, Inc., Cary, NC) was used for statistical analysis, with statistical significance set at a *P* value less than 0.05.

RESULTS

Twenty participants were included in this study. The procedure outlined in this study was completed (Fig. 3). The participants, averaging 40.2 ± 12.5 years of age, underwent analysis before and after cooling interventions (Table 1). The initial superficial finger temperature measured 36.129° ± 0.299°C and significantly decreased to 24.043° ± 1.735°C postcooling, as presented in Figure 4. Notably, there was a substantial reduction in the blood vessel area within the finger, dropping from 13% ± 2.6% before cooling to 3.73% ± 1.2% afterward, indicating a significant difference (mean difference 8.7; 95% confidence interval, 7.85–10.3; $P < 0.001$) (Figs. 5, 6). Similarly, the initial temperature of the superficial hand was recorded as 36.29° ± 0.245°C, decreasing significantly to 23.219° ± 0.961°C postcooling ($P < 0.001$) (Fig. 4). This shift occurred with a considerable decrease in the blood vessel area from 11.2% ± 2.88% before cooling to 3.848% ± 1.621% postcooling (mean difference 13.071; 95% confidence interval, 12.57–13.57; $P < 0.001$) (Fig. 6). Before cooling, the movement of blood cells was predominantly categorized as slow (52.4%) or fast (47.6%). Following the cooling intervention, there was a significant shift in RBC movement, with only 23.8% exhibiting slow movement and the majority (76.2%) showing no movement ($P < 0.001$). **(See Video [online]**, which displays the videocapillaroscopy observations during cooling. The movement of RBCs decreased, and blood vessels were constricted after cooling in

Table 1. Demographics and Changes in Temperature and RBC Movement With Finger and Hand Cooling

Baseline Patient Characteristics	
Age, y*	40.2 ± 12.6
Sex	
Male	9
Female	12
Finger cooling*	
Presurface temperature	36.1 ± 0.3
Postsurface temperature	24.0 ± 1.7
Pre-RBC movement (0 = none, 1 = slow, 2 = fast)	1.1 ± 0.4
Post-RBC movement (0 = none, 1 = slow, 3 = fast)	0.3 ± 0.5
Hand cooling*	
Presurface temperature	36.3 ± 0.2
Postsurface temperature	23.2 ± 1.0
Pre-RBC movement (0 = none, 1 = slow, 2 = fast)	1.5 ± 0.5
Post-RBC movement (0 = none, 1 = slow, 3 = fast)	0.3 ± 0.6

*Mean ± SD.

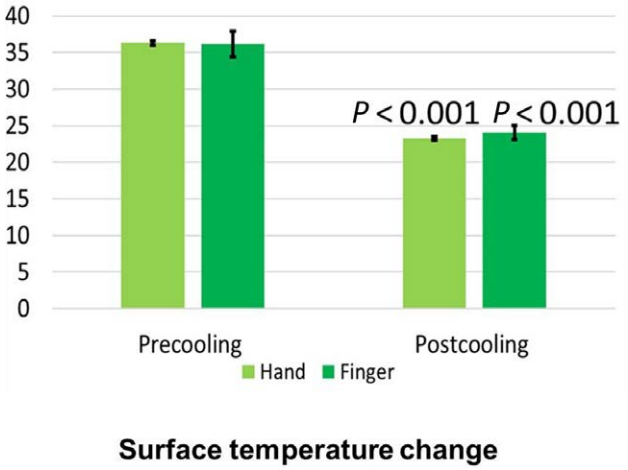

Fig. 4. The cooling procedure reduced the hand surface temperature from 36.4° to 23.4°C and significantly reduced the vascular area. Similarly, the finger surface temperature decreased from 36.5° to 22.5°C, and the vascular area decreased significantly.

both the dorsal hand and nail capillaries.) Postcooling effects included temporary redness and pain, reported by 38.1% and 28.6% of the participants, respectively, within 30 minutes. However, both symptoms resolved within a day, indicating transient discomfort following the cooling procedure (Table 2). These findings collectively demonstrated significant alterations in superficial temperatures, blood vessel areas, and RBC movement after cooling interventions, highlighting the physiological responses induced by the cooling process.

DISCUSSION

To ultimately establish a safe cooling therapy for CIPN, this study first developed a device that can cool at 15°C, a safe temperature for muscle cooling during exercise, based on previous reports. To confirm device safety, we performed hand cooling on healthy volunteers using the docetaxel protocol, primarily used for chemotherapy.

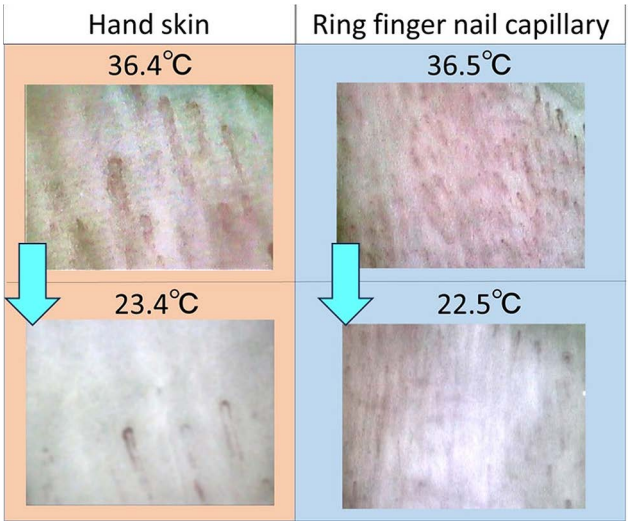

Fig. 5. A remarkable shift commenced at an initial superficial finger temperature of 36.129° ± 0.299°C, demonstrating a significant decrease to 24.043° ± 1.735°C postcooling. This compelling thermal modulation underscores the cooling intervention's efficacy, resulting in a noteworthy reduction in the surface temperature of both hands and fingers.

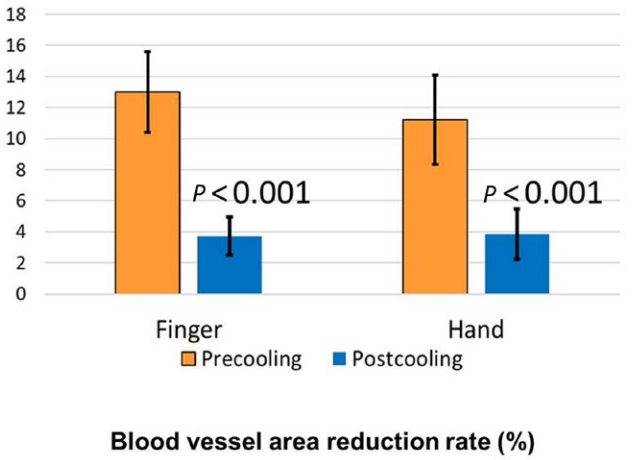

Fig. 6. The initial blood vessel area shifted substantially from 11.2% ± 2.88% before cooling to 3.848% ± 1.621% postcooling ($P < 0.001$). Cooling reduced the vascular area significantly in the hands and fingers.

Table 2. Incidence of Complications Immediately and 1 Week After Cooling Treatment

Complication	Post Half Hour Complication (%)	Post 1 Wk Complication (%)
Temporary redness	38.1	0
Pain	49.8	0
Sensory deprivation	0	0

Based on our experiments, the CECS proved that the device can safely decrease peripheral blood flow without long-term complications. Previous reports have long been

unclear about the appropriate temperatures and systems that allow for safe, uncomplicated cooling and reliably reduce peripheral blood flow.[11,12] Therefore, this study is novel, as it is the first to use videocapillaroscopy to evaluate the resulting reduction in peripheral blood flow in real time using the appropriate cooling temperature for cryotherapy.

Studies on scalp cooling to prevent chemotherapy-induced alopecia have shown that initiating cooling 30–45 minutes before chemotherapy is significant for neuroprotection by vasoconstriction.[21]

Therefore, it has been hypothesized that cooling during and after chemotherapy administration, as well as preventing chemotherapy-induced alopecia, could prevent CIPN, and several studies have been performed on this aspect. To date, 3 of 4 studies in the relatively large category of cooling degrees of −20° to −30°C have shown a preventive effect on CIPN but reported dropout rates of more than 75% due to frostbite resulting from complications associated with cooling therapy.[22–25]

Thus, previous studies have been unclear about how much cooling is needed to prevent CIPN and whether such cooling therapy can be safely implemented, with unclear evaluation methods. Therefore, there is an urgent need to evaluate the degree of peripheral blood flow reduction in real time to adequately prevent CIPN through safe, accurate, and continuous cooling at a constant temperature without causing frostbite.

Therefore, we focused on videocapillaroscopy. Videocapillaroscopy is a tool that has long been used to stage patients with collagen disease and serves as a device to observe the state of capillaries and blood flow in the nail.[26] Observing nail capillaries, particularly on the left fourth finger, has become common because of its reliability in yielding unbiased observations.[27,28] The reason is that the left hand is less likely to be dominant than the right. The fourth finger experiences less frequent usage than the first and second fingers, resulting in lower risks of injury or inflammation and allowing for less biased observations. None of the participants in this study were left-handed, and all were right-handed. Consequently, we observed nail capillaries in the left fourth finger. All the patients were observed without any complications. We observed the central part of the dorsal hand because the palmar side is frequently used, and some subjects had hard skin on the palmar side. We chose the central area because of the tight adherence of the cooling sheet to the hand, which minimized the likelihood of temperature differences. The generated images can be transferred as real-time videos to a personal computer monitor, and graphics for the flow velocity measurements can be shared and recorded. In recent years, its accuracy has improved, allowing detailed measurement of blood flow in the epidermal layer as well as in the capillaries of the nail.[19] The videocapillaroscopy used in this study allows real-time observation at up to 620× magnification at a depth of 1 mm. Our research team has successfully used this device to assess the state of blood flow in the superficial layers of the skin and observe blood flow dynamics in various tissues. The device is noninvasive and has the advantage of being easy to use, requiring no special training. In the preliminary stage of this study, videocapillaroscopy was used to observe skin capillaries in the outer thighs, forearms, axillary midline, abdomen, and fingertips of 20 healthy Japanese subjects to confirm that it is possible to observe cooling-induced changes in skin blood flow. In this study, the epidermis was cooled using ice packs, and the reduction in vascular area and blood flow velocity were successfully measured.[20] Observations showed that the cooling stopped the movement of RBCs, and the vasodilation rate significantly decreased, clearly proving that peripheral blood flow decreased. Hence, the effect of cooling therapy with CIPN could be evaluated in real time.

Another important factor influencing the therapeutic effect of hypothermia on chemotherapy-induced toxicity is the treatment protocol used. Studies on scalp cooling have shown that initiating cooling 30–45 minutes before chemotherapy administration is significant for neuroprotection by vasoconstriction.[21] After maximal cooling, the tissue acquires thermal stability, highlighting the importance of achieving this state before the start of chemotherapy.

Docetaxel is an anticancer drug that causes CIPN. Therefore, we designed a primary treatment model based on a protocol for docetaxel administration.

The observed side effects, such as pain and redness during cooling, were temporary, disappeared within a day, and reliably reduced peripheral blood flow without any sequelae. These results indicate a very safe and reliable reduction in peripheral blood flow compared with reports of extreme cooling leading to frostbite and suggest the potential safety of cooling therapy for patients with CIPN.

Our study used a 15°C cooling device, significantly warmer than previous −15 °C methods, to safely reduce peripheral blood flow without causing frostbite. This result suggests effective CIPN prevention with a lower risk of tissue damage, marking a significant advancement in cooling therapy. Furthermore, the cooling device developed for this study was a circulating chilled-water system weighing 1.7 kg that could be used repeatedly for US $300 per unit. This device is advantageous in terms of safety, portability, and cost-effectiveness. It maintains a constant temperature without the risk of excessive cooling and is simple to use; it simply connects to a power source and switches it on. The sheet does not need to be changed during use and has been proven to be a practical and clinically applicable tool.

The limitations of this study include its proof-of-concept design, which focused on confirming the device safety, and the lack of data on whether CECS can prevent CIPN in actual patients. In addition, the sample size was small. Furthermore, the effectiveness of cooling protocols for various anticancer agents that cause CIPN, particularly those with longer dosing times, such as cisplatin, has not been confirmed for transient side effects such as redness and pain. However, these findings need to be validated in larger randomized prospective studies. In this study, only the cooling of the left hand was evaluated. Because the CECS, a sheet-type device, was designed primarily to evaluate the hands and feet, we plan to conduct

similar experiments and evaluations on the feet in subsequent studies. An ongoing study aimed to collect more detailed data and establish a safe and effective cooling protocol.

As mentioned in the Introduction, cooling therapy for CIPN initially utilized frozen gloves at temperatures ranging from −20° to −30°C. However, this approach results in frostbite, leading to a global recall. Consequently, many patients continue to experience CIPN. However, safe and optimal cooling temperatures remain unknown, and patients cannot receive the potential benefits of cooling therapy.

Frostbite is tissue damage caused by freezing temperatures and is a significant cause of morbidity in cold and high-altitude areas. The direct effects of the freezing temperature include tissue freezing, electrolyte shifts, pH changes, and microvascular damage, ultimately leading to cell death. Inflammatory reperfusion injury and thrombosis can cause tissue damage during rewarming. According to several studies and case reports, many patients experience long-term sequelae after frostbite, including vasomotor disturbances (associated with susceptibility to refreezing), neuropathic pain, nociceptive pain, and damage to skeletal structures. Damage to the microvasculature leads to ischemia, tissue damage, and necrosis, which worsen over time. When the skin is rewarmed, injury leads to inflammation, vasoconstriction, thrombosis, vascular occlusion, blister formation, tissue damage, and necrosis.[29] The study aimed to avoid the risk of frostbite and reduce peripheral blood flow, thereby decreasing the transfer of anticancer drugs to the periphery. After using CECS, RBC movement decreased, and vasoconstriction was observed, confirming the reduced blood flow to the periphery. After the body temperature recovered after cooling, there were no cases of persistent erythema, blister formation, nerve damage, sensory insensitivity, or other after-effects, and no cases of typical symptoms of frostbite. This result suggests that CECS cooling does not promote tissue damage, similar to frostbite, and can be safely limited to the duration of chemotherapy.

This occurrence has given rise to great public interest in the safety of cooling therapy. Therefore, our study aimed to create a safe device for constant-cooling therapy and to investigate its safety and appropriate cooling temperatures. In this study, we chose not to include patients undergoing chemotherapy but first established a safety evaluation phase. We believe that this approach is an appropriate research plan, considering social and ethical considerations. With the confirmed device safety, we are currently administering the same cooling treatment to patients and are gathering favorable data. We intend to report these findings in a second report in future studies. Although opportunities for chemotherapy within the field of plastic surgery are typically limited, the advanced capabilities of videocapillaroscopy, which enables real-time recording and evaluation of blood flow at a depth of 1 mm, offer numerous potential applications in plastic surgery.[1–3] This study proposes one such application of this technology, which we believe will be of great interest to plastic surgeons engaged in clinical, in vivo, and other basic research fields (**see Video [online]**).

Thus, cooling therapy with CECS improves the patients' quality of life during and after cancer treatment, helps avoid chemotherapy dose reductions, and may be promising for preventing CIPN.

CONCLUSIONS

The CECS has demonstrated its capability to provide reliable and sustainable cooling at 15°C, emerging as a valuable tool in preventing CIPN without the risk of frostbite. The findings of this study, including notable vasoconstriction and altered RBC dynamics postcooling, underscore the physiological mechanisms through which the CECS may effectively mitigate CIPN. These results contribute to a clearer understanding of safe and effective cooling temperatures for CIPN prevention, which has remained ambiguous in previous research. However, it is essential to consider the limitations of this study, such as the sample size and focus on a healthy population. Future research should explore the long-term effectiveness of CECS in diverse patient groups and compare its efficacy with other cooling methods. In conclusion, CECS presents a promising avenue for CIPN prevention, warranting further investigation to fully ascertain its clinical utility and broader applicability.

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DISCLOSURES

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ETHICAL APPROVAL

The study was approved by the institutional review board.

DECLARATION OF HELSINKI

This investigation was conducted according to the principles expressed in the Declaration of Helsinki.

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