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Research Article

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Introduction of a Portable and Non-Invasive Technology for Hand and Foot Cooling: a Preclinical Feasibility Study

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Abstract

Introduction: *Chemotherapy-induced peripheral neuropathy (CIPN) is caused by damage to neural structures in distal limbs. CIPN can lead to reduced dose or cessation of chemotherapy. Cryotherapy has shown to be effective in reducing or preventing CIPN in the hands/feet. However, when using ice bath or ice gloves/socks there is no way to maintain the targeted temperature and prevent ice from melting. Also, patients have difficulty tolerating the freezing temperatures over long periods of chemotherapy. The aim of this study was to test the cooling performance of a recently developed non-invasive system that can ultimately replace current cooling methods.*

Materials and Methods: *COOLPREVENT circulates cold water at tolerable temperatures into malleable gloves/socks that does not require replacing of melted ice. We administered a cooling protocol via COOLPREVENT on three healthy subjects for 60 minutes. Immediately before and after cooling, skin temperature in the hands and feet were measured. Level of discomfort was also recorded during the cooling process.*

Results: *Results showed that COOLPREVENT reduces skin temperature by 14.5±3.8°C and 10.7±1.7°C in the hands and feet, respectively within 60 minutes without significant discomfort.*

Conclusion: *Although our study is limited by the small number of subjects and participation of healthy individuals, but we can conclude that COOLPREVENT can be a safe and appropriate method for hand and foot cooling in a uniform manner. We hope that these preliminary findings can pave the way to designing clinical trials we plan to conduct in the near future.*

Keywords: Cancer, Chemotherapy, Chemotherapy-Induced Peripheral Neuropathy, Cooling, Cryotherapy, Hypothermia, Peripheral Neuropathy.

Introduction

In the last 20 years, cancer has emerged among the leading causes of mortality world-wide [1,2]. The number of cancer survivors is expected to increase in the coming years due to the development of sensitive tests for detecting cancer and the administration of front-line chemotherapeutic agents. Although such treatment is intended to target cancer cells, it also affects healthy cells in the body. As a result, profound side effects in almost all patients arise leading to a decrease in the quality of life of cancer survivors [3,4]. Ultimately, clinicians are forced to modify patient's treatment schedule by reducing dosing or early termination of therapy. These events, in turn, lower the efficacy of chemotherapy with a high risk of reduced survival rates.

There are different side effects that have been reported in patients undergoing chemotherapy such as nerve damage, oral mucositis, impact on bone marrow, nausea, exhaustion and hair loss [2-6]. Peripheral nerve impairment, especially in the hands and feet, is known as chemotherapy-induced peripheral neuropathy (CIPN). Symptoms such as loss of sensation, burning, numbness and pain which affects both hands and feet and may spread into a 'glove/stocking' distribution increases the potential risk of falls and occurrence of cuts and burns [2-9]. Patients can also have difficulties with fine motor skills, which makes it hard to perform everyday tasks such as buttoning shirts, brushing teeth and typing on a phone [7-10]. CIPN is a frequent, dose-dependent complication of anticancer drugs, including platinums, taxanes, epothilones, vinca alkaloids, and newer agents, such as bortezomib [11]. CIPN occurs in ~20% of patients given standard doses of chemotherapy and in over 80% of patients treated with high doses [2,9,12].

Different therapeutic drugs have been tested to alleviate CIPN symptoms, but none have shown clinical efficacy. Antidepressants, duloxetine, gabapentin, and a topical gel containing baclofen, amitriptyline, ketamine, lidocaine, tramadol, tapentadol, buprenorphine, and lithium are prescribed to relieve neuropathic pain in other conditions [13-22]. However, since the clinical pathology of CIPN differs, the efficacy is not comparable. As such, the American Society of Clinical Oncology (ASCO), a leading organization that serves as a reference for cancer care, does not recommend any drugs that can act as a gold standard for treatment of CIPN symptoms [13].

Localized cooling or cryotherapy is a non-pharmaceutical method that uses application of ice in the form of gloves and socks has shown to be promising in preventing CIPN [7,23,24]. Based on the available evidence, BrainCool AB, a Swedish medical device company has developed COOLPREVENT that is a prototype cooling system. It is a mechanical system that cools the hands and feet in a controlled, convenient, cost-effective and tolerable manner. Consisting of two components (ECU200 pump-assisted circulatory water unit and COOLIMB attachments for placing over the hands and feet), COOLPREVENT will potentially be a cooling-based solution for the prevention of CIPN. COOLPREVENT circulates cold water (as low as 10°C) into COOLIMB attachments for as long as three hours (Figure 1).

Prior to finalizing the COOLPREVENT system design and initiating clinical trials in the oncology setting, we aimed at investigating the cooling performance of the COOLPREVENT prototype. For this purpose, we conducted a preclinical feasibility study looking at the cooling capability of the COOLPREVENT system and its comfort in healthy individuals. More specifically, we looked at: a) temperature comparison of different areas on the distal limbs before and after a 60 minute period of cooling while COOLPREVENT was set at 10°C, b) whether healthy individuals reported any sensation of pain or discomfort in the hands and feet at different time points while receiving cooling.

Materials and Methods

Three healthy (1 female, average age = 33.7, SD = 6.1) volunteers with no history of sensory, motor and neurological impairment or any medical complications that would prevent them from participating consented to taking part in this study. They were seated in a comfortable chair at 21°C room temperature and were asked to take their socks off and have their hands to above wrists bared. Participants were given ten minutes to allow skin temperature to adapt to the environmental temperature. At this point skin temperature of the thumbs, dorsum (back of hand) and palm of the hands, and dorsum (the area facing upwards while standing), planum (the area facing downwards while standing) of the feet and inside and outside of the ankles were measured using the FLIR thermography camera (FLIR E60, FLIR® Systems AB, Sweden). Cooling gloves and socks were worn by each individual and a footrest was placed under the subjects' feet to avoid any restriction of water flow in the cooling socks (Figure 1). The ECU200 pump was set at 10°C and the cooling period started. At the 60 minutes time point the gloves and socks were taken off and skin temperature was immediately measured on the previously mentioned areas (Figure 2). The thermography camera was positioned such that it captured the highest temperature at the centre of designated areas, depicted by a white squared selection in images (Figure 2). Study administrators were trained to ensure that measurement points were kept as consistent as possible across different subjects.

Ideally, it would have been beneficial to measure skin temperature during the cooling period to investigate how the skin adapts to the low temperatures. However, the water-filled gloves and socks acted as a thick layer over the skin and thus the thermography camera could not make reliable recording of skin temperature during the cooling process. Pain quantity was measured using the numerical pain rating scale (NPRS) from zero to ten, with zero being no pain at all and ten being the most pain ever experienced by subjects. Pain levels and area of pain were recorded at 0, 30- and 55-minute time points during cooling.

Figure 1. Current prototype design of the COOLPREVENT system application for the treatment of chemotherapy-induced peripheral neuropathy (CIPN). Patients will be seated in a comfortable chair with a footrest positioned under their lower legs. Patients will be wearing cooling gloves and socks (COOLIMB attachments) and water coming from the cooling unit will circulate through COOLIMB attachments to lower skin temperature in the distal limbs.

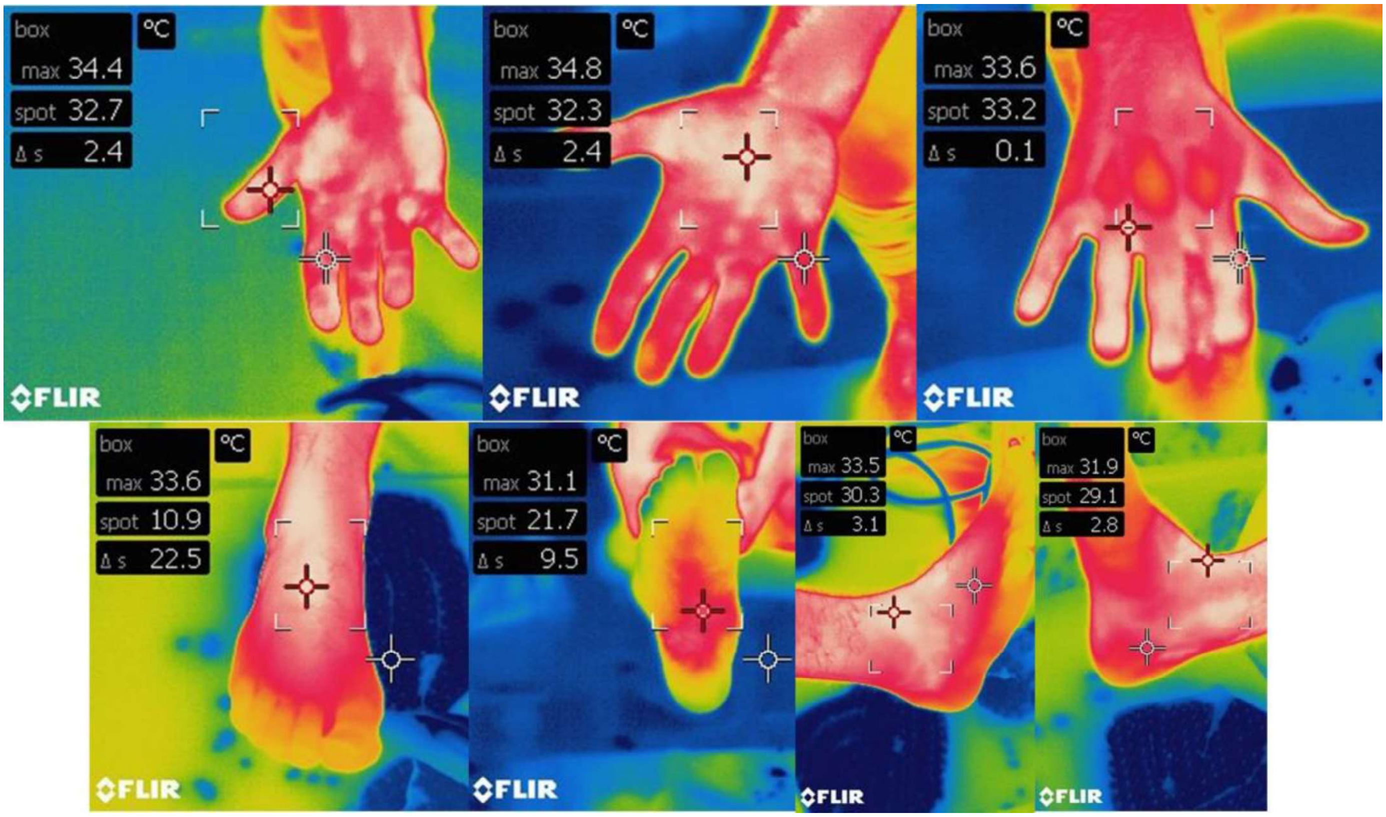

Figure 2. Images of temperature measurements of an exemplary subject for different areas of the hand and foot. Top panel shows measurements for the thumb, palm and dorsum of the right hand. Bottom panel shows measurements for the dorsum, planum, inside and outside of the right foot. Note that the highest temperature in the square selection in the center of each body area was recorded.

Results

Tables 1 and 2 show temperature measurements across right and left hands and feet, respectively for each subject, as well as average measures with associated standard deviations. To simplify comparison in before and after measures, it was decided to report average values on one area of the right hand and foot. Specifically, the right thumb and planum surface of the right foot was selected.

Table 1. Temperature measurements (°C) across hand areas. Average measurements with standard deviations (SD) are also presented.

	Hands											
	Right						Left					
	Dorsum		Palmar		Thumb		Dorsum		Palmar		Thumb	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Subject 1	33.4	20.9	35.1	31.6	34.4	16.3	32.3	20	34.6	27.9	34.7	15.4
Subject 2	33.6	21.9	34.8	21.5	34.3	19.5	33.3	20.2	34.9	24	33.2	16.7
Subject 3	32.5	20.6	33.8	23.8	33.3	22.7	33.5	23	34.3	28.7	33.7	18.1
Average (SD)	**33.2 (0.6)**	**21.1 (0.7)**	**34.6 (0.7)**	**25.6 (5.3)**	**34.0 (0.6)**	**19.5 (3.2)**	**33.0 (0.6)**	**21.1 (1.7)**	**34.6 (0.3)**	**26.9 (2.5)**	**33.9 (0.8)**	**16.7 (1.35)**

Table 2. Temperature measurements (°C) across foot areas. Average measurements with standard deviations (SD) are also presented.

	Feet															
	Right								Left							
	Dorsum		Planum		Inside		Outside		Dorsum		Planum		Inside		Outside	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Subject 1	31.3	20	28.3	19.3	30.3	17.4	31.9	16.2	31.8	22.4	28.7	19	31.4	18	31.9	17.5
Subject 2	33.6	20.1	31.2	20.5	31.9	19.3	33.5	16.7	32.7	16.1	30.1	19.4	31.2	20.2	32.8	16.1
Subject 3	32.3	14.3	28.7	16.3	30.6	15.6	31.9	17.4	31.8	15.3	27.9	17.3	29	14.5	31	16.9
Average (SD)	**32.4 (1.2)**	**18.1 (3.3)**	**29.4 (1.6)**	**18.7 (2.2)**	**30.9 (0.85)**	**17.4 (1.85)**	**32.4 (0.92)**	**16.8 (0.6)**	**32.1 (0.5)**	**17.9 (3.9)**	**28.9 (1.1)**	**18.6 (1.1)**	**30.5 (1.3)**	**17.6 (2.9)**	**31.9 (0.9)**	**16.8 (0.7)**

Figure 3 demonstrates temperature measurements in the right hand and foot separately for all three subjects. Looking at average values, the temperature in the right thumb dropped by 14.5±3.8°C (34.0°C to 19.5°C) while in the planum surface of the right foot it dropped by 10.7±1.7°C (29.4°C to 18.7°C). See Figure 4 for a graphical depiction of average temperature drops in the right hand and foot following 60 minutes of cooling. According to the recorded pain ratings, on average individuals reported 0, 2, and 3 out of 10 pain in the hands at 5, 30 and 55 minutes of cooling, respectively and 7, 4.5, and 5.8 out of 10 pain in the feet at 5, 30 and 55 minutes of cooling, respectively (Table 3).

Table 3. Average rating and location of pain in the hands and feet at each time point. All subjects reported an equal amount of pain rating in both hands or both feet.

	5 minutes		30 minutes		55 minutes	
	Hands	Feet	Hands	Feet	Hands	Feet
Subject 1	0	0	0	0	0	0
Subject 2	0	0	2/10 Dorsum of hands	4/10 Dorsum of feet	3/10 Dorsum of hands	5/10 All over feet
Subject 3	0	7/10 Dorsum of feet	0	5/10 All over feet	0	6.5/10 All over feet
Average	**0**	**7/10**	**2/10**	**4.5/10**	**3/10**	**5.8/10**

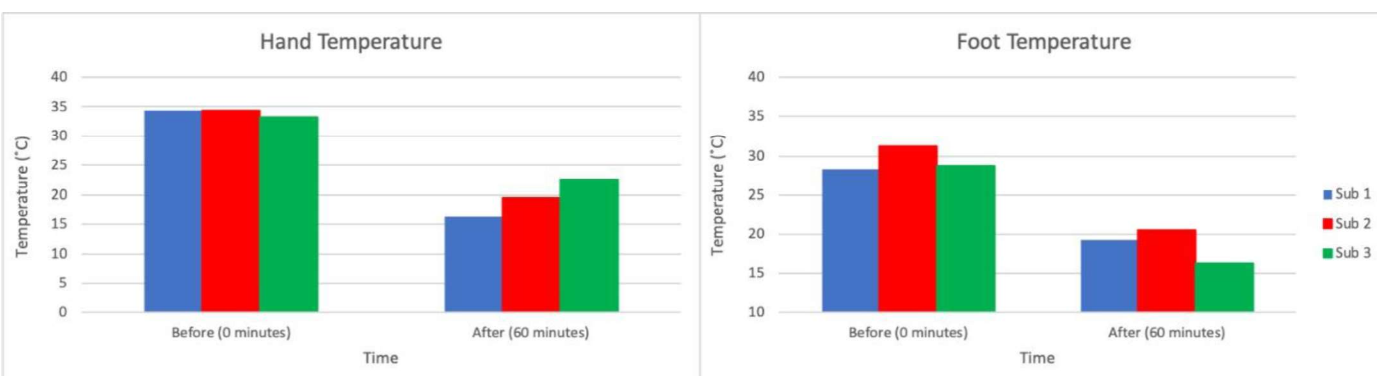

Figure 3. Temperature measurements (°C) across the three subjects immediately before and after cooling process. Note that values reflect temperature of the the right thumb in the left panel and the planum surface of the right foot in the right panel.

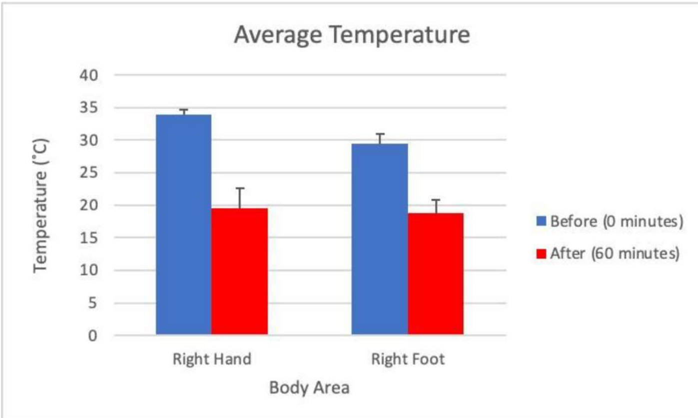

Figure 4. Average temperature measurements (°C) across three subjects before and after 60 minutes of cooling. Note that measurements for the right thumb and planum surface of right foot have been selected for simplicity. Error bars represent one standard deviation for each measurement.

Discussion

Chemotherapeutics are effective in arresting the progression of cancer as they are often designed to differentially target and eliminate rapidly dividing cancer cells. Despite the positive effects of chemotherapeutic approaches in the cancer-fighting arena, there are also various deleterious side effects such as pain, hair loss, fatigue and CIPN that negatively affect normal cells and structures of the body.Up to now, three different avenues for treating CIPN and its associated symptoms have been explored: pharmaceutical drugs, cryotherapy using ice and mechanical cooling devices. Therapeutic agents are designed to relieve neuropathic pain in conditions such as diabetes which differ in their pathophysiology when compared to CIPN. Therefore, no drugs to date have proven effective in treating CIPN, as outlines by ASCO [13]. Cryotherapy using crushed ice or freezing gloves and socks is the common method of cooling that has demonstrated promising findings for treating CIPN. In this method patients are encouraged to wear frozen gloves and socks or submerge their limbs into crushed ice buckets while receiving chemotherapy. However, the main disadvantage is the high number of withdrawals from the study due to extreme low and intolerable temperatures (-20 to -30 °C) that prevents patients from completing the cryotherapy cycle [7,11,12,25-27]. As well, using these methods are limited in terms of time as the ice starts to melt and loose its cooling capacity.

With regards to cryotherapy using technical devices, to our knowledge two devices have been introduced, Hilotherm's cooling and Paxman's cryocompression systems. The Paxman device is currently in the design and development phase and a "Beta" prototype has not been finalized at this point [28]. An ongoing clinical trial (N=64) conducted on the Hilotherm device was recently published [29]. Patients from breast, gynaecological and pancreatic cancer population undergoing chemotherapy with paclitaxel, paclitaxel/carboplatin, and nab-paclitaxel/Gemcitabine were included. According to this study, the Hilotherm cooling device functioned in a closed-loop circuit with coolant (set at 10°C) flowing in mittens and socks that patients wore during their drug infusion. Results demonstrated that patients tolerated the cooling process well throughout the treatment session and they did not develop advanced levels of CIPN. Follow up results regarding CIPN development after chemotherapy cessation are not yet reported. In this study, the technical specifications of the device have not been described but the two cooling units (one for hands and one for feet) and its cooling pads are cumbersome and cooling mittens are not designed such that they can provide uniform cooling around the hands. Additionally, skin temperature values in the hands and feet were not measured. Thus, it is unclear what the skin temperature reached and whether cooling was distributed evenly around the distal limbs using this device.

Therefore, localized cryotherapy is a method which has demonstrated clinical efficacy and is hypothesized to lead to a cascade of events. In other words, cryotherapy will bring down tissue temperature causing vasoconstriction of blood vessels in distal limbs. The reduction of blood flow to the hands and feet will slow down metabolism and prevent chemotherapeutic agents from penetrating the capillaries which means that there is less damage incurred by nerve fiber endings in the hands and feet and ultimately preventing the risk of CIPN [7,30]. Thus, there is an urgent need for a technique that can deliver cryotherapy to the patient in a controlled and tolerable manner.

To answer to this need, BrainCool AB has developed COOLPREVENT, a mechanical cooling prototype that cools the hands and feet in a uniform, convenient, and tolerable manner. In this preclinical project we intended to verify the cooling performance and comfort of the COOLPREVENT system prototype on healthy volunteers. The results demonstrate that COOLPREVENT can reduce skin temperature by 14.5±3.8°C and 10.7±1.7°C in the hands and feet, respectively. The discomfort reported by subjects was to the extent that it did not cause intolerable pain and subjects were able to complete the cooling process for 60 minutes. Based on the findings of this study COOLPREVENT is: a) Tolerable for individuals- COOLIMB attachments will allow hands and feet temperatures to drop for a minimum of 10°C during 60 minutes of cooling. b) Controllable and convenient to implement in the treatment room- by being ice-free (no-melting, no need for clean-up) c) Convenient in size and distributes cooling evenly around all regions of the hands and feet. According to our preliminary findings, we hope that COOLPREVENT can potentially provide protection against CIPN offered by cryotherapy. It is expected that reduction in these side-effects will in turn lead to higher treatment compliance with increased survival rates of patients with cancer and improved quality of life during and after treatment.

The main limitation of the current study was the small number of participants. The study was conducted on three healthy subjects and thus results should be interpreted with caution. To be able to make more reliable statements regarding cryotherapy using COOLPREVENT, large number of patients undergoing chemotherapy must be tested.

In conclusion, results from this preclinical feasibility study are promising and demonstrate that the COOLPREVENT prototype system can be administered to reduce skin temperature by at least 10°C. Our future goal is to validate the use of COOLPREVENT in clinical trials with the intention of using this system to prevent or treat CIPN in patients undergoing chemotherapy.

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Authors' contributions:

Conception and design: all authors. Acquisition of data: S Davarpanah Jazi, M. FazelBakhsheshi. Analysis and interpretation of data: S Davarpanah Jazi. Drafting the article: S Davarpanah Jazi. Critically revising the article: M FazelBakhsheshi and J. Ralf. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: M. Fazel Bakhsheshi. Study supervision: S Davarpanah Jazi

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