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

Shirin Davarpanah Jazi

BrainCool AB

Johan Ralf

Polarcool AB

Mohammad FazelBakhsheshi (✉ mohammad.fazel@braincool.se)

Lund University: Lunds Universitet <https://orcid.org/0000-0001-5013-8284>

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Abstract

Purpose: 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. Cooling the hands/feet has shown to be effective in reducing or preventing CIPN. However, when using ice bath or ice gloves/socks 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.

Methods: COOLPREVENT circulates cold water at tolerable temperatures into malleable gloves/socks. As well, COOLPREVENT 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 reduce skin temperature by $14.5 \pm 3.8^\circ\text{C}$ and $10.7 \pm 1.7^\circ\text{C}$ 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. We hope that these preliminary findings can pave the way to designing clinical trials we plan to conduct in the near future.

Introduction

Cancer is a major cause of mortality worldwide and the number of deaths due to cancer is on the rise. In the last 20 years, cancer has emerged among the leading causes of mortality world-wide (1, 2) and the number of cancer survivors is expected to increase in the coming years due to the increasing development of sensitive tests for detecting cancer and the administration of frontline 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 which can lead to reduction in 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, 3, 4).

One of these mentioned side effects is damage to peripheral nerves in the body specially the hands and feet, known as chemotherapy-induced peripheral neuropathy (CIPN). Symptoms such as loss of sensation, burning, numbness and pain in the hands and feet have been reported which can increase the risk of fall injuries and occurrence of cuts and burns (2, 5, 6). Patients can also have difficulties with fine motor skills, which makes it difficult to perform everyday tasks such as buttoning shirts, brushing teeth and typing on a phone (5, 7).

Localized cooling is a method which has demonstrated clinical efficacy in reducing blood flow to the hands and feet, bringing down tissue temperature and ultimately preventing CIPN (for review see 5,8 and 9). BrainCool AB, an established Swedish medical device company with a rich portfolio of medical cooling devices, has developed a prototype cooling system. COOLPREVENT is a mechanical cooling 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 the hands and feet), COOLPREVENT will 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. See Fig. 1 for a schematic depiction of the COOLPREVENT system.

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 1- temperature comparison of different areas on the distal limbs before and after a 60 minute period of cooling while cooling unit was set at 10°C , 2- 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 degrees 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). As shown in Fig. 1, 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. 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 shows temperature measurement points for different areas of the hands and feet in an exemplary subject before cooling period started. 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 in Fig. 2). Study administrators were trained to ensure that measurement points were kept as consistent as possible across different subjects. The amount of pain or discomfort 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 were recorded at 0, 30- and 55-minute time points during cooling and if individuals reported any pain or discomfort, they were asked to describe the area of their pain on a human discomfort drawing provided to them.

Results

Tables 1 and 2 show temperature measurements across hands and feet, respectively for all subjects, 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, in the right hand the thumb and the in the foot the planum surface of the foot was selected. 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 $14.5 \pm 3.8^{\circ}\text{C}$ (34.0°C to 19.5°C) while in the planum surface of the right foot it dropped by $10.7 \pm 1.7^{\circ}\text{C}$ (29.4°C to 18.7°C). See Fig. 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. For a detailed description of average pain measurement and area of pain at different time points in the hands and feet across all three subjects see Table 3.

Table 1
Temperature measurements ($^{\circ}\text{C}$) for all subjects across different right and left hand areas. Average measurements with associated standard deviations (SD) across three subjects 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 ($^{\circ}\text{C}$) for all subjects across different right and left foot areas. Average measurements with associated standard deviations (SD) across three subjects 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)

Table 3

Average rating and location of pain in the hands and feet for each subject at 5, 30 and 55 minutes of cooling time. Note that the rating was between 0 to 10 with 0 being the sensation of no pain and 10 being the most pain the subjects had ever experienced. 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	4/10	3/10	5/10
			Dorsum of hands	Dorsum of feet	Dorsum of hands	All over feet
Subject 3	0	7/10	0	5/10	0	6.5/10
		Dorsum of feet		All over feet		All over feet
Average	0	7/10	2/10	4.5/10	3/10	5.8/10

Discussion

In this preclinical project we intended to verify the cooling performance and comfort of the COOLPREVENT system prototype developed by BrainCool AB on healthy individuals. The results of this preclinical project demonstrate that COOLPREVENT can reduce skin temperature by $14.5 \pm 3.8^{\circ}\text{C}$ and $10.7 \pm 1.7^{\circ}\text{C}$ 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.

Chemotherapeutics are effective in arresting the progression of cancer because 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. CIPN is a frequent, dose-dependent complication of anticancer drugs, including platinum, taxanes, epothilones, vinca alkaloids, and newer agents, such as bortezomib (10). CIPN not only leads to dose reduction or discontinuation of treatment but also decreases the quality of life of cancer survivors. CIPN occurs in ~20% of patients given standard doses of chemotherapy and in over 80% of patients treated with high doses (2, 11, 12).

CIPN occurs when peripheral nerves are damaged, and presents clinically as deficits in sensory, motor, and sometimes autonomic function. Sensory disturbances range from a mild tingling sensation to spontaneous burning pain and hypersensitivity to stimuli. These symptoms often affect both hands and feet and may spread into a 'glove/stocking' distribution (12). There is currently no preventative treatment that is approved and there are no active medicines to treat CIPN if it occurs. The need is thus great in both general oncology and hematology, and for patients a preventative treatment would be preferable.

Localized cooling is a method which has demonstrated clinical efficacy and is hypothesized to lead to a cascade of events. In other words, cooling will bring down tissue temperature causing vasoconstriction of blood vessels in distal limbs. The reduction of blood flow to the hands and feet means that there is less damage of chemotherapy agents incurred by nerve fiber endings in the hands and feet and ultimately preventing the risk of CIPN (5, 13). However, current methods for inducing cooling are based on the use of ice packs in the form of gloves and socks and ice-water baths to cool the hands and feet; methods which are difficult to control and can therefore be painful and intolerable for patients. As well, using these methods are limited in terms of time as the ice starts to melt and lose its cooling capacity. Thus, there is an urgent need for a technique that can deliver cooling 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 controlled, convenient, and tolerable manner. Based on the findings of this study COOLPREVENT is: 1. Tolerable for individuals- COOLIMB attachments will allow hands and feet temperatures to drop for a minimum of 10°C during 60 minutes of cooling. 2. Controllable and convenient to implement in the treatment room- by being ice-free (no-melting, no need for clean-up). According to our preliminary findings, we hope that COOLPREVENT can potentially provide protection against CIPN offered by cooling. It is expected that reduction in these side-effects will in turn lead to higher treatment compliance with higher survival rates of patients with cancer and improved quality of life during and after treatment.

This study had several limitations. First, as a result of a manufacturing defect in one of the cooling gloves, there was not enough contact between the skin and the cooling material. We have been in communication with the manufacturing company and the issue is being resolved to ensure it does not occur in later stages of clinical testing. Second, this preclinical study was conducted on three healthy subjects and thus results should be interpreted with caution. To be able to make more reliable statements regarding the effect of cooling using COOLPREVENT, larger number of patients undergoing chemotherapy must be tested.

Therefore, 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.

Declarations

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Declaration

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Figures

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 liquid coolant 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.

Figure 3

Temperature measurements (°C) across the three subjects immediately before and after cooling process. Note that values reflect temperature of the thumb of the right hand 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.