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Subjective perceptions of 8, 11 and 14°C chemotherapy liquid cooled gloves and socks

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Abstract

We investigated the effects of peripheral cooling using chemotherapy gloves and socks at three cooling temperatures on subjective perceptions. The hands and feet were cooled with 8, 11, and 14°C by water-perfused gloves or socks. Nine females participated in six experimental conditions: hands or feet cooling at 8, 11, and 14°C. The heat was extracted at 3.8, 5.4, and 7.7 kJ·min^{1} via the gloves and at 4.1, 6.0, and 9.0 kJ·min^{-1} via the socks. While the results showed that overall subjective perceptions did not differ among the three temperatures (~ 9.0 kJ·min^{-1}), there were significant differences in local thermal comfort, pain sensation, and pain discomfort among the three cooling temperatures ($P < 0.05$). When cooling the hands or feet at 8, 11 or 14°C, subjects felt 'cold' or 'cool', on average, at the end of 60-min cooling with no significant differences among the three temperatures, whereas subjects felt more uncomfortable at 8°C than 14°C for cooling either the hands or feet ($P < 0.05$). Subjects felt more pain at 8°C than 14°C cooling for both hands and feet. These results indicate that the 8°C cooling for 60 min might cause uncomfortable pain sensation, especially for cold-vulnerable individuals. We recommend 1) a cooling bout of less than 60 min, 2) a cooling temperature higher than 8oC when cooling the hands or feet, and 3) a higher temperature for the feet when the hands are simultaneously cooled. However, the present results on subjective perceptions should be interpreted with peripheral vasoconstriction of fingers and toes while cooling.

Keywords: Peripheral cooling, Water-perfused gloves and socks, Cooling temperature, Thermal sensation, Thermal comfort, Pain sensation, Pain discomfort

Introduction

Cancer is a serious public health problem all over the world. Annually, more than 1.2 million cancer cases and 500,000 cancer deaths occurred in the United States (Jemal et al., 2008). Over the last 10 years in Korea, the leading cause of death has been cancer accounting for about 27% of deaths (Statistics Korea, 2020). Applied cancer treatments differ from patient to patient. Surgery, radiation therapy, and chemotherapy are common (Miller et al., 2019; Warren et al., 2008). As cancer treatments improve, so do survival rates (Hong et al., 2020). Although anti-cell drugs that kill the fast-growing cells contribute to chemotherapy's effectiveness, these have side effects.

Hand–Foot syndrome which is known as palmar–plantar erythrodysesthesia syndrome (PPE) or chemotherapy-induced peripheral neurotoxicity (CIPN) is the major side effect caused by chemotherapy (Nagore et al., 2000). Common symptoms of Hand–Foot syndrome are numbness, dysesthesia, tingling sensations, and even severe pain in the hands and feet, and rarely on the trunk, neck, chest and scalp (Baack & Burgdorf, 1991; Nagore et al., 2000). Although these side effects are not critical or life-threatening, they may cause inconveniences in daily life because the hands and feet are the most frequently used body parts. Adjusting drug dose could be the first solution to alleviate the side effect of chemotherapy (Abushullaih et al., 2002). The combination of chemotherapy with other therapies such as pyridoxine (vitamin B6) is considered to be effective in delaying and relieving Hand–Foot syndrome (Gordon et al., 1995; Vail et al., 1998). However, most solutions are based on chemical adjustments, and there are relatively few physical interventions to reduce Hand-Foot syndrome. Silva et al. (2020) reviewed scalp cooling during chemotherapy and concluded scalp cooling prevents chemotherapy-induced alopecia.

According to the statistics data reported about the cancer types of the patients, it was confirmed that cancer cells are rarely found on the hands or feet (Jemal et al., 2011). For this reason, submerging the hands and feet in cool water to cause vasoconstriction can be used to reduce drug delivery associated pain in the hands and feet. Bun et al. (2018) reported that hand and foot cooling using frozen gloves and socks was effective to reduce Hand–Foot syndrome. Lassere and Hoff (2004) suggested that pain sensation caused by Hand–Foot syndrome could be relieved by cooling the hands and feet. Molpus et al. (2004) reported that regional cooling relieved the frequency and severity of Hand–Foot syndrome, but most previous studies only tested a single temperature using an ice pack to evaluate the effect of cooling on Hand–Foot Syndrome. However, there is little literature to investigate appropriate cooling temperature on the hands and feet in terms of subjective perception. Cooling with very low temperature causes strong vasoconstriction of the hands and feet and alleviates Hand–Foot syndrome, but patients could be intolerable with strong cold pain on the skin. Even though cooling of the hands and feet showed physiologically significant results for reducing side effects, patients could feel discomfort along with severe pain sensation when their skin was exposed to cold materials (Enander, 1982; Lee et al., 2017). Such prolonged cooling could lead to deterioration of subjective responses to the cooling (Havenith et al., 1992; Morton & Provins, 1960), which could decrease treatment effects. In this regard, it is meaningful to examine effective cooling temperature on reducing physiological side effects, and also reducing severe subjective perceptions due to cooling. The purpose of this study was to investigate effective cooling temperature to alleviate severe subjective perceptions while wearing water-perfused cooling gloves or socks. We hypothesized that peripheral cooling would not have an effect on whole body subjective perceptions. Additionally, subjective perceptions of the hands or feet would be influenced by cooling and showed difference among cooling temperatures.

Methods

Subjects

We recruited nine young healthy Korean females (21.8 ± 2.5 y in age, 161.3 ± 4.6 cm in height, 58.2 ± 8.9 kg in body weight, 23.8 ± 6.2 kg·m^{-2} in body mass index, and 30.6 ± 6.6% body fat). The minimum number of subjects by G-power sample size with the following inputs [Alpha error < 0.05, Power = 0.95, experimental conditions = 3, and repeated measure design] was eight. We recruited nine subjects considering missing cases in the middle of trials. The age of the current subjects might be younger than female patients with cancers in real life, and the young subjects were healthy without any Hand–Foot syndrome, which should be considered when interpreting the results from the present study. The present study was the 1st year experiment of the 3-year grant, and we were supposed to apply the 1st and 2nd year results to female patients with breast or uterine cancers with the cooperation of female cancer medical teams. The subjects visited our laboratory six times and each trial was performed at the same time to neutralize the effects of circadian rhythm. The Latin Square design was applied in order to minimize any possible order effect. All subjects participated during their follicular phase to avoid any effects from their menstrual cycle on core temperature and subjective perception. Subjects were instructed to avoid heavy exercise and alcohol for 24-h prior to each trial and not consume food or caffeine for 3 h prior to each trial. All trials for each subject were completed within four weeks and at least 48 h was separated each visit. Volunteers who might suffer from hyperhidrosis were excluded. All subjects were informed and signed consent forms voluntarily before their participation. The experimental protocols of this study were approved by the Institutional Review Board of Seoul National University (IRB No. 1912/002-007).

Experimental design and procedures

To evaluate the effects of cooling hands or feet at three cooling temperatures on subjective perception, a pair of gloves and socks (outer fabric: polyester 92% & polyurethane 8%, and inner mesh: nylon 85% and polyurethane 15%) was developed (Fig. 1). PVC tubing (4 mm in internal diameter and 6 mm in outside diameter) was inserted in the inner mesh layer to fix the tube position, and to make contact with the skin when worn. In order to make the gloves and socks fit for subjects, we developed various sizes of gloves and socks with an identical design and the same length of tubing. The length of PVC tubing inserted was 3.0 m and 4.2 m for each glove and sock (6.0 m and 8.4 m for a pair of gloves and socks), respectively. Cool water circulator (Model C-332, SIBATA, Japan) was used to maintain particular temperatures, and to pump cooling liquid (propylene glycol and water in a volume ratio of 1:1). The liquid flow rate was 0.85 L min^{-1} both pairs of gloves and socks.

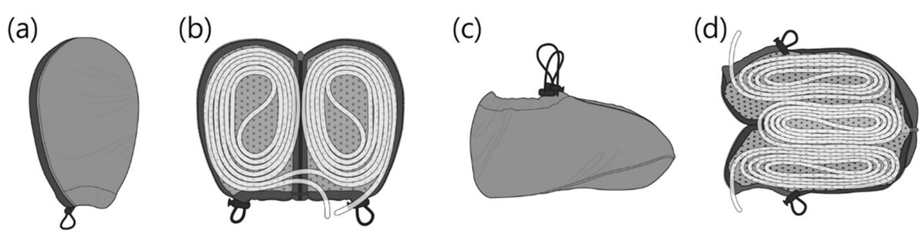

Fig. 1 Schematic images of cooling gloves and socks. External image of a glove (**a**), unfold-internal image of a glove with 3.0 m of PVC tubing of helical forms (**b**), external image of a sock (**c**), and unfold-internal image of a sock with 4.2 m of PVC tubing of helical forms (**d**)

Ambient temperature and humidity of the experimental room was maintained at 23.6 ± 0.5°C and 23 ± 6%RH. The relative humidity was lower than a comfortable value (e.g., 50%RH), but no subject expressed being thirsty or dry because they were on a recliner without any exercise. Subjects wore identical undershorts, long pants, long sleeve shirts, and light jackets (1020 g in total clothing mass). Subjects lay on a recliner during trials starting with 20-min rest for stabilization, followed by wearing either cooling gloves or socks for the next 60 min. We had not considered lower contact temperature than 5°C to avoid any cold-induced vasodilation. Water circulators (baths) were set to circulate the cooling liquid at 0°C, 5°C or 10°C, but the surface temperatures of PVC tubing that touched the skin of the hands and feet were 8°C, 11°C or 14°C, respectively (Table 1). Koscheyev et al. (2007) addressed that rigorous skin cooling was below 14°C, of which the reflex response of the superficial vessels is to conserve heat through skin vasoconstriction. According to this, we considered 14°C as an upper limit of cooling to cause skin vasoconstriction. Lower contact temperatures than 8°C was not feasible for the present experimental devices and glove/socks design because the water temperature of the water bath should have been set at below zero. Starting from 8°C, 3°C-interval between experimental conditions was set because 1–2°C-interval might be too narrow to distinguish subjective responses. The three cooling temperatures when applied to actual cancer patients could be adjusted according to the facilities and patients' conditions. The surface temperature was measured for 60 min. All subjects participated in six experiments with three cooling temperatures for both hands and feet. Hand cooling conditions (HCC) with 0°C, 5°C, and 10°C inlet water and feet cooling conditions (FCC) with 0°C, 5°C, and 10°C inlet water were named 8C-hands, 11C-hands, 14C-hands; and 8C-feet, 11C-feet, 14C-feet. We checked the contact temperatures of 8°C for 60 min was safe enough for subjects through pilot tests and Bun et al. (2018) reported that 45-min wearing gloves and socks frozen at − 22°C for 12 h (and new frozen gloves and socks after the 45-min wearing replaced) was safe for patients.

Measurements

Liquid temperatures from the water circulators flowing through the cooling gloves and socks and the surface temperature of PVC tubing were continuously measured using thermistors (LT-ST08-12, Gram Corporation, Japan) and recorded with a data logger (LT-8A, Gram Corporation, Japan) every 5 s. Heat extraction from the hands or feet to the circulated liquid was calculated with Eq. (1).

$$\text{Heat extraction} = \text{Flow rate} \times \text{Specific heat of liquid} \times \text{Difference in temperature.} \quad (1)$$

Table 1 The surface temperature of PVC tubes according to cooling liquid temperature

	Cooling temperature of the liquid (temperature of water baths)		
	0 ℃	**5** ℃	**10** ℃
Temperature inside gloves	7.8 ± 0.6	10.7 ± 0.6	14.0 ± 0.4
Temperature inside socks	7.5 ± 0.5	10.3 ± 0.6	13.5 ± 0.4
Experimental condition	8C-condition	11C-condition	14C-condition

Heat extraction from the skin (kJ min^{-1}); Flow rate through the gloves and/or socks (L min^{-1}); Specific heat of liquid (3.559 kJ·(kg °C)$^{-1}$); Difference in temperature between inflowing and outflowing liquid temperature (°C).

To evaluate subjective perceptions, subjects were asked about their thermal sensation, thermal comfort, cold pain sensation, and pain discomfort after 10 min of rest and every 10 min after the 5th min from the start of cooling (Fig. 2). A 9-point categorical scale was used to grade thermal sensation (-4: very cold, -3: cold, -2: cool, -1: slightly cool, 0: neutral, 1: slightly warm, 2: warm, 3: hot, 4: very hot) and a 7-point categorical scale was used for thermal comfort (-3: very uncomfortable, -2: uncomfortable, -1: a little uncomfortable, 0: not both, 1: a little comfortable, 2: comfortable, 3: very comfortable). A 6-point categorical scale was used for cold pain sensation (-5: extremely painful, -4: very painful, -3: painful, -2: moderately painful, -1: slightly painful, 0: no pain), and a 6-point categorical scale was used for cold pain discomfort (-4: extremely uncomfortable, -3: very uncomfortable, -2: uncomfortable, -1: a little uncomfortable, 0: not both, 1: a little comfortable). Concerning the pain discomfort, we instructed subjects to distinguish from the pain sensation, itself, or thermal discomfort. On the comfortable categories of the pain discomfort, subjects could choose the #1 (a little comfortable) or #0 (not both) when they did not feel any pain sensation. Distinguishing #1 from #2 was dependent on the subjects. Subjects could choose a mid-point between two consecutive points for all the four scales, which was recorded as a score of '0.5', '1.5' or so. Subjective perceptions

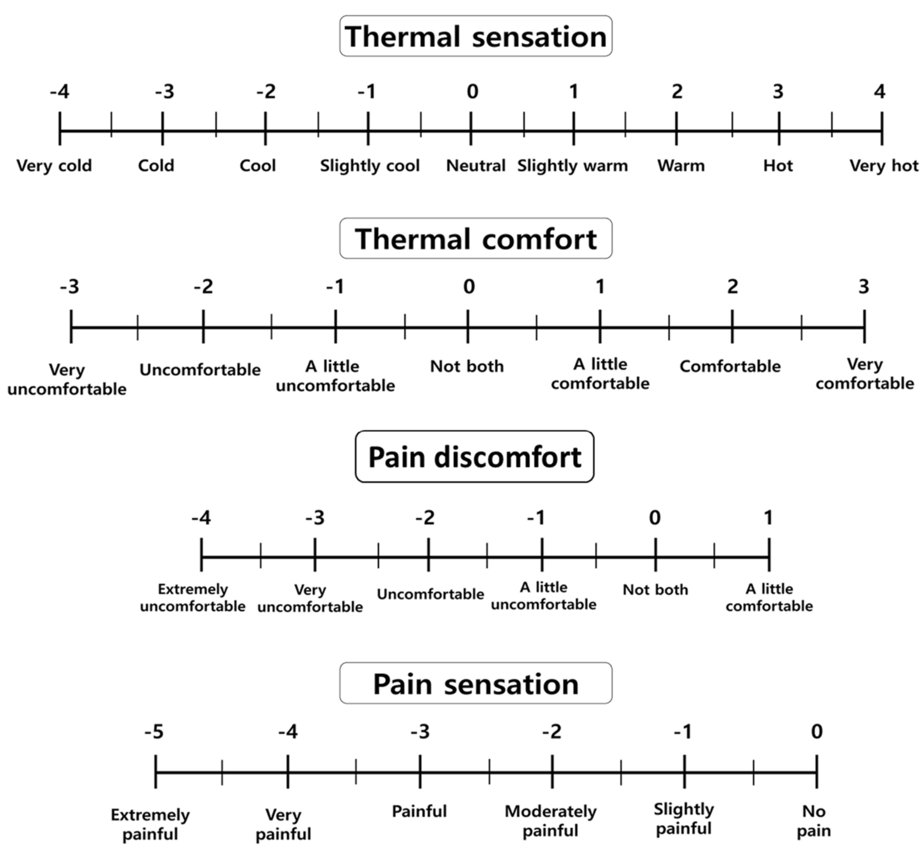

Fig. 2 Subjective scales of thermal sensation, thermal comfort, pain discomfort and pain sensation

on the hands or feet included the subjective responses of the fingers or toes, while finger or toe sensations were limited to the fingers or toes only. Subjective perception on the fingers and toes were additionally asked in order to catch pain sensation or pain relief due to possible cold-induced vasodilation on the fingers and toes.

Data analysis

In the present study, all data were expressed as means with standard errors (mean ± SE). Statistical analyses were performed with SPSS 26. Friedman tests were conducted to confirm differences in subjective perception responses between cooling conditions. One-way analyses of variance (ANOVA) and paired t-test were used to confirm the differences between heat extractions. Duncan's Post-hoc tests were used to identify the parameter that showed significant differences in subjective perceptions and heat extractions. A significance was set at $P < 0.05$.

Results

Heat extraction

For gloves, 8C-hands showed higher heat extraction than 11C-hands or 14C-hands ($P < 0.001$, Table 2; 3.8, 5.4, and 7.7 kJ·min^{-1} via the gloves for the 8°C, 11°C and 14°C, respectively). Likewise, 8C-feet showed significantly higher heat extraction than 11C-feet or 14C-feet ($P < 0.001$, Table 2; 4.1, 6.0, and 9.0 kJ·min^{-1} via the socks for the 8°C, 11°C and 14°C). Feet cooling showed higher heat extraction values than hand cooling for 8C, 11C and 14C (Table 2). However, the results were reversed when the heat extraction was converted by per tubing length (kJ·min^{-1}·m^{-1}). Heat extraction per tubing meter was higher for hand-cooling than for feet-cooling in all 8C, 11C and 14C (Table 2).

Whole body thermal sensation and comfort

At rest, no significant differences were found between the six cooling conditions for all subjective perceptions (Fig. 3). Subjects felt thermally neutral to slightly cool (Fig. 3a), neither comfortable nor uncomfortable (Fig. 3b, d), and no thermal pain (Fig. 3c).

Local thermal sensation and thermal comfort

There were no significant differences in local thermal sensation among the three cooling temperatures for both HCC and FCC, expressing 'cool', on average, over the hands or

Table 2 Heat extraction and heat extraction per PVC tubing meter of cooling conditions

		8C-condition	11C-condition	14C-condition	*p-value* †
Temperature difference between outlet and inlet water temperatures (℃)	Hands	2.5 ± 0.1*	1.8 ± 0.0**	1.2 ± 0.1**	$p < 0.001$
	Feet	3.0 ± 0.2	2.0 ± 0.1	1.3 ± 0.0	$p < 0.001$
Heat extraction (kJ·min^{-1})	Hands	7.7 ± 0.4*	5.4 ± 0.1**	3.8 ± 0.2**	$p < 0.001$
	Feet	9.0 ± 0.4	6.0 ± 0.2	4.1 ± 0.1	$p < 0.001$
Heat extraction per tubing meter (kJ·min^{-1}·m^{-1})	Hands	1.3 ± 0.1*	0.9 ± 0.0***	0.6 ± 0.0***	$p < 0.001$
	Feet	1.1 ± 0.1	0.7 ± 0.0	0.5 ± 0.0	$p < 0.001$

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$: Significant differences of heat extractions between the hands and feet. †Heat extractions between 8C-hands, 11C-hands, and 14C-hands, or between 8C-feet, 11C-feet, and 14C-feet were significantly different ($p < 0.001$)

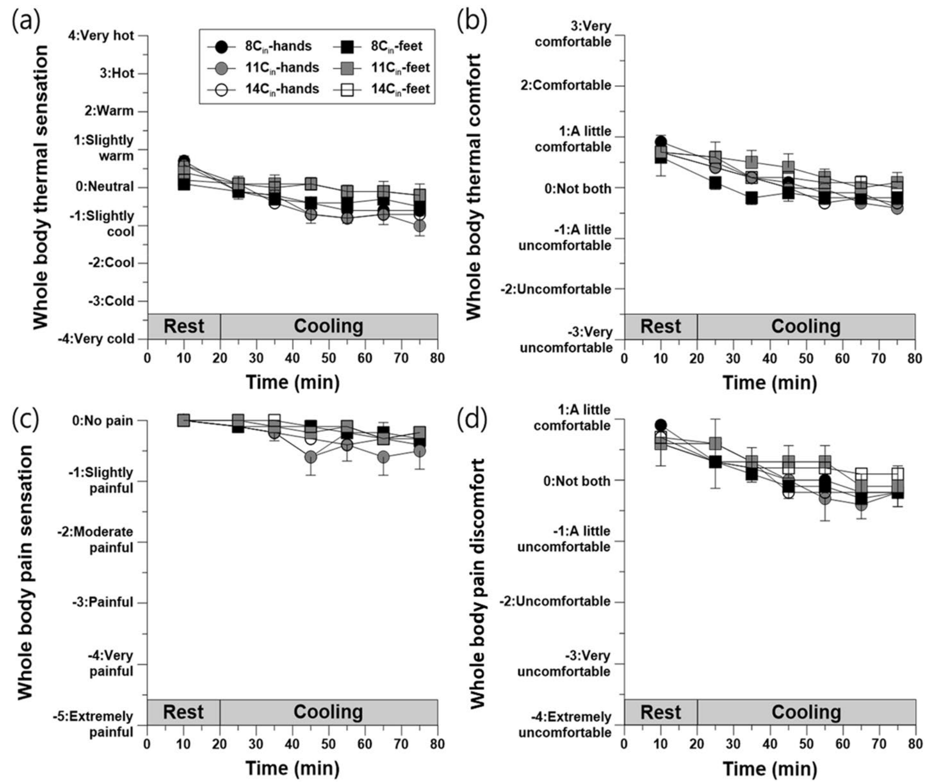

Fig. 3 Whole body subjective perceptions of hands/feet cooling at 8, 11, and 14°C. Thermal sensation (**a**), thermal comfort (**b**), cold pain sensation (**c**), and pain discomfort (**d**) (mean ± SE, N = 9)

the feet (Fig. 4a, c) and 'between cool and cold', on average, over the fingers and toes. For HCC (8C-hands, 11C-hands, and 14C-hands), thermal sensation of the hands and fingers gradually decreased when cooling began and maintained from 50 to 60th min, while for FCC (8C-feet, 11C-feet, and 14C-feet) thermal sensation of the hands and fingers maintained similar values as values at rest (Fig. 4a, b). The thermal sensation of feet and toes were significantly lower for FCC than for HCC ($P < 0.001$, Fig. 4c, d; e.g., toe thermal sensation at 55th min [Mean ± SD]: − 0.3 ± 0.9 for 8C-hand vs. − 2.8 ± 0.8 for 8C-feet).

While cooling, significant differences in local thermal comfort between the three cooling temperatures were found, showing that 8C-hands had lower thermal comfort on the hands than 14C-hands at 35th, 45th, and 55th min (Fig. 5a; e.g., hand thermal comfort at 55th min [Mean ± SD]: − 1.1 ± 0.6 for 8C-hand vs. − 0.8 ± 0.8 for 14C-hand). But no significant differences between 8 and 11C-conditions or 11C and 14C-conditions were found. There were no significant differences among the three temperatures in finger thermal comfort for HCC; and thermal comfort of the toes and feet for FCC were not significantly different (Fig. 5b–d). Even at the end of the 60-min cooling, local thermal discomfort over the hands or feet was not degraded than being 'uncomfortable'.

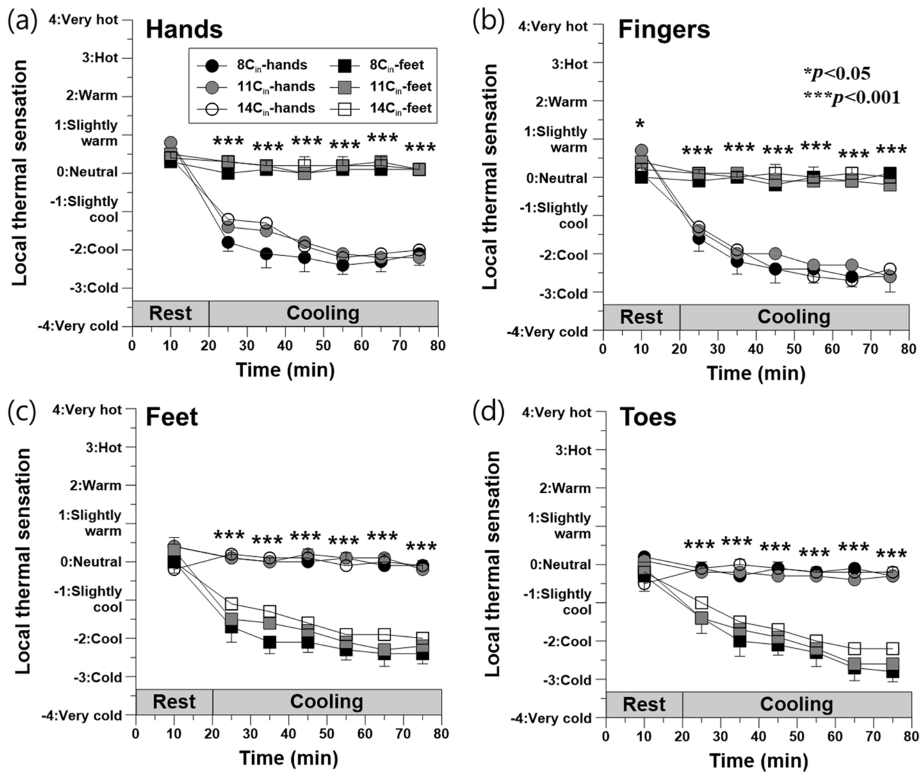

Fig. 4 Local thermal sensation of hands/feet cooling at 8, 11, and 14°C. Hands (**a**), fingers (**b**), feet (**c**), and toes (**d**) (mean ± SE, N = 9). * and *** represent statistical differences between hands and feet conditions at each cooling temperature

Local cold pain sensation and pain discomfort

There were significant differences in local cold pain sensation among the three cooling temperatures for both HCC and FCC. Hand and finger pain sensation in 8C-hands and 14C-hands were on average 'slightly painful' and 'moderately painful', respectively ($P < 0.001$, Fig. 6a, b; e.g., finger pain sensation at 55th min [Mean ± SD]: − 1.7 ± 1.1 for 8C-hand vs. − 1.2 ± 0.9 for 14C-hand). Likewise, 8C-feet triggered more foot and toe pain sensation than 14C-feet ($P < 0.001$, Fig. 6c, d; e.g., toe pain sensation at 55th min [Mean ± SD]: − 2.1 ± 0.6 for 8C-feet vs. − 1.1 ± 0.5 for 14C-feet). With the passing of cooling time, pain sensation was more reinforced on the hands and fingers for HCC and the feet and toes for FCC until the first 40-min cooling (Fig. 6). The pain discomfort of the hands and fingers for HCC were significantly different with 8C-hands and 11C-hands during cooling and 14C-hands showed significant differences between the 45th min and 75th min (Fig. 7a, b). On the feet and toes, subjects gradually expressed uncomfortable sensation during FCC (Fig. 7c, d). No significant difference between the pain sensation of the feet and toes for FCC from 45 to 75th min was found.

Heat extraction and thermal comfort, cold pain sensation and pain discomfort

Subjects found lower (degraded) local thermal comfort, pain sensation and pain discomfort for the feet when feet cooling had higher heat extraction, whereas hand subjective perceptions during the hand cooling were similar for 11°C and 8°C cooling

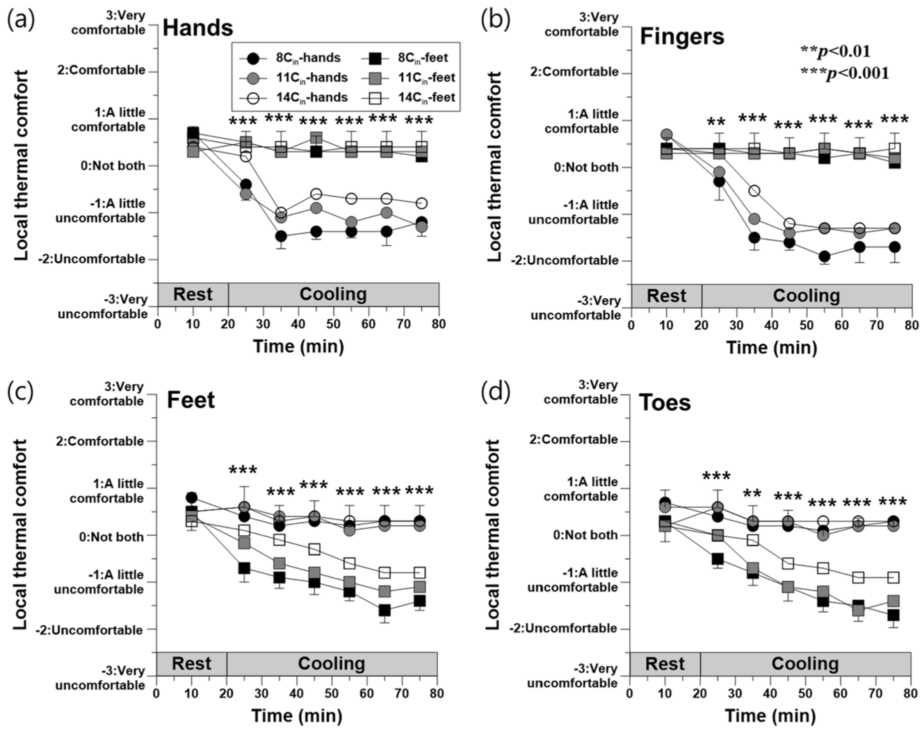

Fig. 5 Local thermal comfort of hands/feet cooling at 8, 11, and 14°C. Hands (**a**), fingers (**b**), feet (**c**), and toes (**d**) (mean ± SE, N = 9). ** and *** represent statistical differences between hands and feet conditions at each cooling temperature

(Fig. 8). In more detail, local subjective perceptions during the 8°C-hands cooling were similar to those during the 11°C-feet cooling even though heat extraction was 2 kJ·min^{-1} higher for 8°C-hands than 11°C-feet (Fig. 8).

Discussion

In order to reduce the acute side effects of chemotherapy, the hands and feet can be cooled for patients while receiving anticancer treatments in hospitals. In the present study, we evaluated the effects of the three particular cooling temperatures on the overall and local subjective perceptions of the subjects. The following major findings are discussed. Firstly, cooling of the hands or feet did not have any significant effect on whole body subjective perception, and local pain sensation on the hands and feet was on average 'moderately painful' at the end of 60-min exposure. These findings indicate that the three cooling levels in the present study were tolerable for the subjects because the category 'moderately painful' in the local pain sensation corresponded to subjective responses ranging from 'a little uncomfortable' and 'uncomfortable', rather than expressing 'very uncomfortable', in terms of local pain discomfort. Secondly, the skin cooling temperature at 8°C was distinguished from 14°C cooling in terms of local subjective perceptions. Thirdly, subjective perceptions of the feet during the 8°C-feet cooling resulted in greater changes than subjective perceptions of the hands during the 8°C-hand cooling, while 11°C and 14°C cooling of hands and feet induced similar subjective sensations.

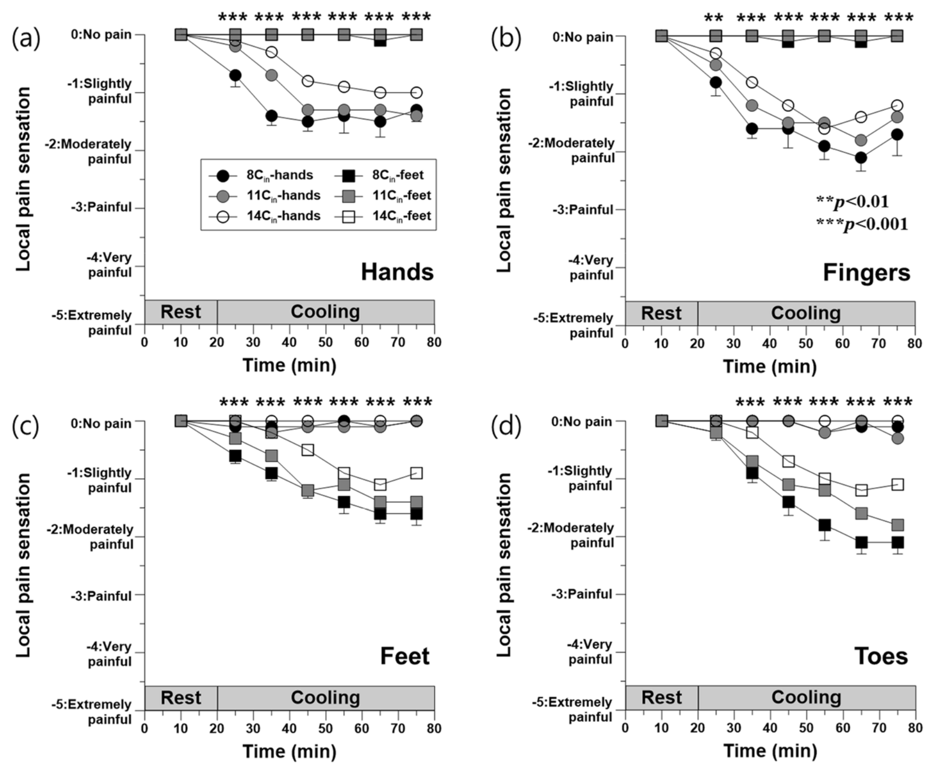

Fig. 6 Local pain sensation of hands/feet cooling at 8, 11, and 14°C. Hands (**a**), fingers (**b**), feet (**c**), and toes (**d**) (Mean ± SE, N = 9). ** and *** represent statistical differences between hands and feet conditions at each cooling temperature

In the present study, the effects of the three particular cooling temperatures were evaluated in terms of subjective perceptions, but the actual effectiveness of the three temperature levels should be examined by the peripheral vasoconstriction of cancer patients while receiving chemotherapy. Therefore, the discussion below is limited to the effects of contact cooling temperatures on subjective responses of healthy young women.

Periphery cooling with max. 9 kJ·min^{-1} does not affect overall thermal sensation and comfort

We found no significant difference in whole body subjective perceptions among 8, 11, and 14°C cooling of the hands or feet. Similar levels of whole body perception were found at rest and during cooling (Fig. 3). These finding are consistent with previous reports. Overall subjective perceptions did not show any significant difference among 10, 15 and 20°C head cooling (Shin et al., 2015). Nakamura et al. (2013) reported that limb cooling in hot conditions and warming in cold conditions showed no effect on overall thermal comfort. Thermal stimulation that was applied to the limbs had little effect on whole body thermal sensation (Cotter & Taylor, 2005). When subjects immersed their middle finger in cold water (4°C), their overall thermal comfort was similar at rest (no immersion) and during cold water immersion (Ko et al., 2020). However, there are also studies that are inconsistent with the present results. Both

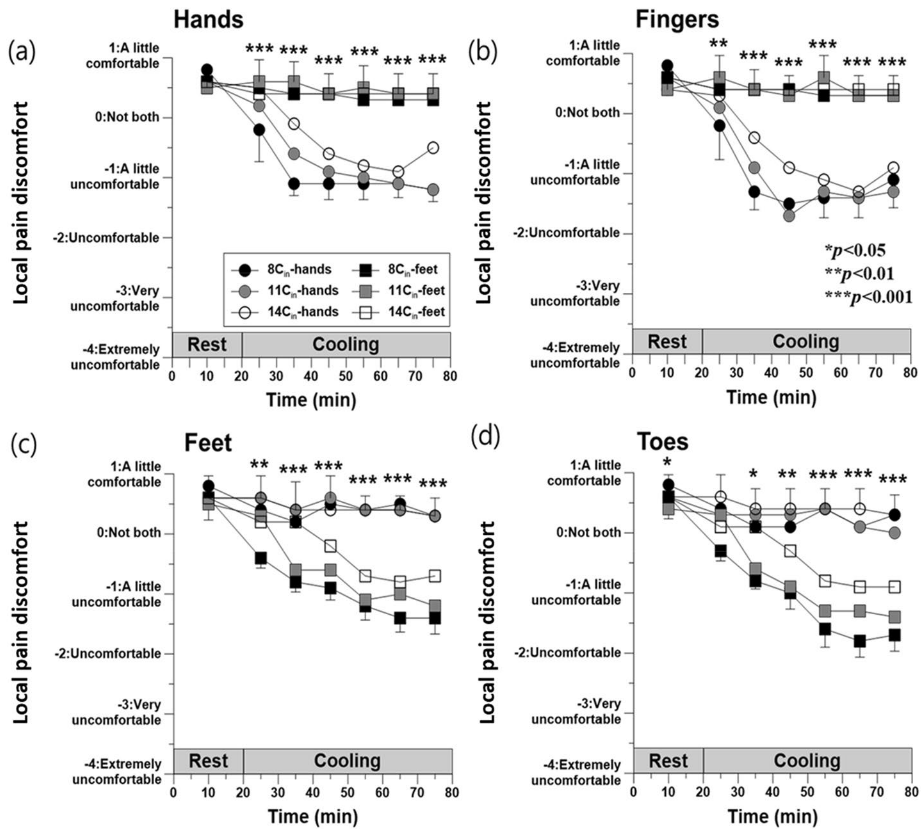

Fig. 7 Local pain discomfort of hands/feet cooling at 8, 11, and 14℃. Hands (**a**), fingers (**b**), feet (**c**), and toes (**d**) (mean ± SE, N = 9). *, **, and *** represent statistical differences between hands and feet conditions at each cooling temperature

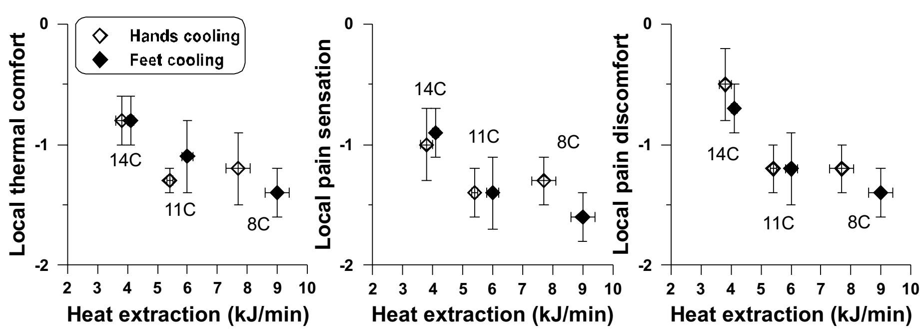

Fig. 8 Relationships between heat extraction and local thermal comfort, pain sensation and pain discomfort at 8, 11, and 14℃. In the graphs, 'local body' represents the hands for hand cooling and the feet for feet cooling. Data are expressed as mean ± SE (N = 9). The number of categories are '0 not both', '− 1 a little uncomfortable', and '− 2 uncomfortable' for comfort; and '0 no pain', '− 1 slightly painful', and '− 2 moderately painful' for cold pain sensation

back and head (neck) cooling efficiently improved thermal sensation and thermal comfort in hot environments (Lan et al., 2018). Likewise, cooling one of the torso parts (the chest, abdomen, upper back, or lower back) significantly improved overall thermal sensation and thermal comfort at 28, 30 and 32°C (Yang et al., 2019). Taken the present and previous results together, peripheral cooling with a heat of extraction of ~ 9 kJ·min^{-1} might not have a negative effect on whole body subjective perceptions.

Secondly, the role of cutaneous thermosensitivity on overall and local perceptions can be discussed. Cutaneous thermosensitivity evoked sensory responses (Cabanac et al., 1972). According to previous studies, it is known that cutaneous thermal sensitivity is not uniform and depends on the body region (Nakamura et al., 2008; Zhang et al., 2004). The face had a higher density of thermal receptors than other body regions (Stevens & Choo, 1998; Stevens et al., 1974), while extremities are generally the least sensitive (Crawshaw et al., 1975; Luo et al., 2020; Taylor & Gayton, 1986). Even though the hands and feet are the peripheral body regions, the feet are less sensitive in detecting cutaneous thermal stimuli (Lee et al., 2010, 2011). For whole body thermal comfort, facial cooling was the most effective during mild heat exposure, while trunk warming was more preferred than the facial warming in cold (Nakamura et al., 2008). Extremities are commonly considered to be the least effective regions for determining whole body thermal sensation (Cotter & Taylor, 2005). To summarize, the cooling of the hands and feet might be less effective in changing whole body thermal perceptions because the hands and feet are less thermally sensitive compared to the face or trunk.

Heat extraction from the hands or feet

The hands and feet are considered as two of the most effective body regions for alleviating heat strain using external cooling (House et al., 1997; Livingstone et al., 1995). In this study, PVC tubing was inserted in a water-perfused glove (3.0 m per glove, 6.0 m for a pair of gloves) and a sock (4.2 m per sock, 8.4 m for pair of gloves). Cooling socks contained longer PVC tubing and more covered the feet, nearly 6.8% of body surface area, whereas cooling gloves contained shorter tubing and less covered the hands, 4.9% of body surface area (Lee & Choi, 2009). For this reason, foot cooling was more efficient in extracting stored heat (kJ·min^{-1}) than hand cooling using the same temperature liquid (Table 2). On the other hand, heat extraction per PVC tubing meter (kJ·min^{-1}·m^{-1}) showed the opposite results with being higher for the hand cooling than for the foot cooling. Skin blood flow to the hands was up to 3–4 times greater than that of the feet (Taylor et al., 2009). Greater skin blood flow could allow for more heat transfer via the hands. In this study, the largest heat removal was found at the 8 ℃-condition for both hands and feet. Subsequent research can examine the relationship between heat extraction and the skin blood flow of the hands or feet.

Local subjective perceptions at 8°C and 14°C cooling

Which temperature between 8 to 14°C would be appropriate for chemotherapy patients in terms of subjective perceptions? It is no wonder that the most important determinant for choosing a cooling temperature is peripheral vasoconstriction which is evaluated in terms of skin blood flow. However, once a certain degree of peripheral vasoconstriction is achieved, patients' subjective perception should be considered. Koscheyev et al. (2007) suggested a total of 11 principles concerning physiological design of liquid cooling and warming garments. The first principle was that different body tissues transfer heat in/out of the body in different manners. Body regions with complex vessel networks, like the fingers and toes are preferable for rapid heat transfer. The third principle was that the body does not cool down efficiently at very low temperatures because the reflex response of the superficial vessels is to conserve heat. Following this principle, a mild cooling (18–20°C) regime is more effective to extract body heat than rigorous cooling (14°C) under heat stress. The aim of the present study was the opposite of Koscheyev et al. (2007). Our mission was to determine cooling temperature to induce effective vasoconstriction with no severe pain sensation, whereas Koscheyev et al. (2007) aimed to find optimal cooling temperature to remove effectively the body heat from the periphery, not causing vasoconstriction. In this light, we consider 14°C as an upper limit of cooling to cause skin vasoconstriction, and compared 14, 11, and 8°C cooling. We found that local thermal comfort and pain sensation of the hands and feet at the 8°C cooling were inferior to local thermal comfort and pain sensation at 14°C cooling. That is, subjects felt colder and more thermally uncomfortable with stronger pain sensation in the hands at 8°C than at 11 or 14°C and similar responses were found for the feet. However, because the average value of pain sensation was kept around 'moderately painful' even at the end of 60-min exposure, 8°C cooling was not noxious for subjects.

One more issue to discuss is whether or not the cooling temperature for the hands and feet of cancer patients receiving chemotherapy should be identical as the present results. Based on the present results, we recommend slightly higher cooling temperature (e.g., 2–3°C higher) on the feet than on the hand, in terms of subjective perception and the larger surface area of feet, for intensive cooling of both hands and feet simultaneously. Differences between the hand and foot cooling temperature can be determined according to patients' preferences. This recommendation could be justified in fact that the cooled surface area of the feet (6.8% of body surface area according to Lee and Choi 2009) is larger than the cooled area of the hands (4.9% of body surface area according to Lee and Choi 2009), which is reflected in the total tubing length of the gloves and socks in the present study. The difference in heat extraction due to the difference in tubing length between the gloves and socks was found at the 8°C cooling, rather than at 11 or 14°C cooling. However, this recommendation based on subjective perceptions should be taken and interpreted together with peripheral skin vasoconstriction of the fingers and toes for local cooling.

Conclusions

Whole body subjective perceptions were not affected by the 8°C-cooling for an hour (~9.0 kJ·min^{-1} in heat extraction). Local thermal discomfort, pain sensation, and pain discomfort in the hands and feet were more degraded at 8°C-cooling than at 14°C-cooling, but responses during the 11°C-cooling were not distinguished from either 8°C- or 14°C-cooling results. Local pain sensation during the local cooling were maintained at 'moderately painful' on average, even at the end of 60-min exposure of the 8°C-cooling. These results imply that the heat extraction of approximately ~9 kJ·min^{-1} from the periphery is acceptable in terms of cold pain discomfort. However, further studies with a sufficient number of older patients with cancer while receiving chemotherapy are required to validate the present results obtained from young healthy females. From practical persepectives, we have to consider the simultaneous cooling of the hands and feet, as well as patients and ageing. In the present study, we cooled the hands and the feet, separately, but the permissible cooling temperature might be higher than 8°C in case of simultaneous cooling both the hands and the feet. In order to validate the present results, cancer patients' peripheral vasoconstriction or cold-induced vasodilation of the fingers and toes while cooling at various low temperatures should be explored.

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Authors' contributions
SH participated in experiment, data analysis and carried out discussion and drafted the manuscript. YJ participated in experiment, data analysis and discussion. HL, DS, CH participated in experiment and data analysis. JY devised study plan and participated data analysis, discussion and managed manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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