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Impact of daily cooling treatment on skin inflammation in patients with chronic venous disease

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Abstract

People with chronic venous disease are at high risk for developing venous leg ulcers. Inflammation is posited as a pathological factor for this chronic condition as evidenced by persistently elevated skin temperature. As part of a larger trial to test the effects of a cooling regimen on leg ulcer prevention, the objective of this preliminary study was to evaluate the first 30 days of intense daily cooling. Compared to a placebo control cuff, a gel cuff applied to the most severely affected lower leg skin for 30 minutes daily showed no statistically significant differences between temperatures taken in the home at baseline compared to those measured at the 1 month follow up visit. There were also no differences in temperatures noted between the two groups, although the temperatures in the treatment group were lower 30 minutes after treatment, an indication of adherence. There was no discernable decrease or increase in temperature at a given time point during the 30 day treatment period compared to the control group. It may be better to

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have patients monitor skin temperature on a daily basis and then apply the cuff as necessary, rather than requiring daily cooling based on baseline measurement. This “prn” approach may provide a sufficient cooling milieu to prevent escalation of inflammation and thwart ulcer occurrence or recurrence.

Clinical trials registration #NCT01509599

Keywords

Skin temperature; Local cooling; Chronic venous disease; Inflammation

Introduction

Leg ulcers are a serious problem for individuals with chronic venous disease (CVD). Over 70% of all lower extremity leg ulcers are of venous origin and almost 1/3 become chronic [1]. While there is no consensus on the primary etiology of chronic leg ulcers, one theory posits an aberrant inflammatory state as a causative factor [2]. Early in the disease process, venous hypertension increases the size and permeability of dermal venules and arterioles that lead to extravasation, or leakage of fluid and electrolytes, plasma proteins, and macromolecules such as fibrinogen into the dermis, the second layer of the skin [3]. The extravasated fluid and macromolecules initiate a cascade of inflammatory reactions, including leukocyte activation that increases metabolic activity in the affected areas of skin [4]. Over time, inflammation causes varying degrees of injury to the vessels, tissues and skin, and lengthens the healing process [5, 6]. When the inflammatory process itself becomes prolonged, skin damage, such as venous eczema (redness and itching), hyperpigmentation (brown discoloration), lipodermatosclerosis (hardening), and slow-to-heal or non-healing venous leg ulcers (VLUs) arise [6].

Our previous studies have described skin temperature elevation and patterns of temperature variability of CVD-inflamed skin, measured with validated infrared- and thermistor-type thermometers at the gaiter area of affected lower legs [7]. We found that skin temperature was elevated by ~1-2°C compared to unaffected contralateral skin and the lower leg skin of healthy controls [8]. In another study, we hypothesized there would be discernable hour-to-hour or day-to-day skin temperature variations of affected skin compared to unaffected skin [9]; however no pattern was observed. These findings suggest that normal “rise and fall” fluctuations or variability in the skin's thermoregulatory response to external stimuli (e.g., bathing) and internal mechanism (e.g., exercise) is altered. We concluded that skin temperature remains consistently elevated, however, a sudden spike in this “flat lined” temperature pattern over a 24-hour period is predictive of venous ulceration [10]. The persistently elevated temperatures and lack of variability suggest inflammation may play a key role in the disease process, postulated to be responsible for the skin damage that results in chronic ulcers [11]. Thus, directly cooling the inflamed skin may provide a therapeutic option to ameliorate the negative sequelae of prolonged inflammation [12]. The data reported here are skin temperature measured on the first 30 days of an intensive cooling regimen targeting chronically inflamed lower leg skin.

Materials and Methods

To investigate the variability in skin temperature in response to cryotherapy, a repeated measures design compared skin temperatures of affected (treatment leg) skin in 99 subjects randomized to the treatment group that used a cooling gel cuff and the control group that used a placebo cotton cuff applied to the lower leg.

Subjects

Individuals ages 21 and above with a diagnosis of CVD were recruited from four study sites in Georgia and South Carolina, USA. The study protocol was approved by the Medical University of South Carolina's Institutional Review Board. All subjects signed informed consent prior to being screened, were assigned to either the cooling treatment or control placebo group via stratified permuted block randomization, and received \$175 for participation. Inclusion criteria were: CEAP Classification for Chronic Venous Disease [14] stages C4 (skin damage) or 5 (healed venous leg ulcer within past two weeks up to two years). Since arterial circulation might influence the effect of cooling on skin blood flow, only subjects with ankle brachial index (ABI) of 0.8 to 1.3 mmHg, were included. Subjects without intact temperature sensory discrimination (measured with TipTherm® [Axon, Duesseldorf]) and pressure perception (measured with a monofilament) were excluded due to concern that the presence of neuropathy or the inability to sense changes in temperature could increase risk of harm, such as frostbite. This risk was deemed minimal.

All subjects agreed to follow the cooling treatment protocol (30 minutes a day), wear a compression wrap (JuxtaLite, CircAid by medi, San Diego, CA) on the treatment leg during waking hours, elevate both legs while performing the treatment, measure daily leg skin temperatures with a long handled infrared dermal thermometer before and after the treatments and then 12 hours later, record temperatures on specially designed logs, and attend a follow-up clinic visit at the end of the first month.

Procedures

At the baseline clinic visit, subjects were given study instructions and materials, and viewed a short instructional DVD about study procedures. Baseline lower leg skin temperatures, measured 5 cm above the medial malleolus were recorded with the thermistor (PeriFlux 5020 Temperature Unit, Perimed, Stockholm, Sweden) which has previously been shown to demonstrate a high level of agreement with the infrared thermometer (TempTouch, Diabetica Solutions, San Antonio, TX) used in this study [7, 15]. Demographic data, vital signs, and the medical history were also collected.

The treatment leg had the most severe clinical signs such as eczema, darker pigmentation, harder skin, larger surface area affected, and/or one or more healed ulcers at the ankle “gaiter” area between the malleoli and bottom of the calf muscle. This is the area of skin at which VLU commonly occur and was marked with a surgical skin marker so that subjects knew where to measure their skin temperature when they returned home.

At home, subjects measured and recorded skin temperature over the marked spot. The daily treatments were performed mostly in the evening. The 12-hour post treatment temperatures

were generally taken in the morning. During waking hours, the compression wrap was worn on the treatment leg and removed during the treatment.

The gel treatment and placebo cotton control cuffs were designed and manufactured specifically for this study by Southwest Technologies, Kansas City, MO. Cuffs were available in four sizes (small, medium, large, extra large), size based on the ankle circumference. Cuffs were kept in the freezer set to -18°C until the time of use. The cotton cuff warmed to room temperature within two minutes of removal from the freezer whereas the gel cuff maintained its cooling properties for upwards of one hour as noted in a consistent reduction in microcirculatory blood flow [16].

Data collection and analysis

Experimental data included the three daily home skin temperature measurements. Skin temperature in the clinic was measured during the baseline and month 1 return clinic visit by study personnel. All study data were managed using the Research Electronic Data Capture (REDCap) Survey and Database tool. Data were analyzed with SAS software (SAS version 9.3, Cary, North Carolina) with statistical significance maintained at an alpha level of 0.05.

The four study aims were analyzed using the following statistical analyses:

Aim 1 examined differences between clinic and home measurements obtained at baseline and the month 1 return clinic visit. The initial (average of first three days of home temperatures) and last (average of last three days of temperatures) of the morning leg temperature readings obtained from the subjects' daily skin temperature logs of the treatment legs, after removing measurements outside of the possible range ($<22^{\circ}\text{C}$, $>36^{\circ}\text{C}$) were assessed using Bland-Altman plots.

Aim 2 examined the three home temperature measurements between groups to observe adherence to the treatment protocol. Trends (e.g., variations in day-to-day treatment leg temperatures) between the groups for these three measurements were assessed using Spaghetti plots. A decrease in temperatures after cooling in the treatment group as compared to the control group was considered evidence of adherence to the treatment protocol.

Aim 3 sought to establish the length of time in days that the daily cooling treatment was required to reduce skin temperature variability and thus stabilize skin temperatures. Decreased variability was an indication that the metabolic activity (inflammation) in the skin was responding to the cooling therapy. Generalized linear mixed models were used to determine whether a statistically and clinically significant reduction, or “drop” in skin temperature was achieved in the treatment groups' legs compared to the control groups' legs. Longitudinal measurements were assessed for spline effects.

Aim 4 explored relationships among temperatures, demographic (covariates) and clinical variables by treatment group. Multivariate linear regression models were used to investigate putative relationships of baseline demographic and clinical variables with temperature at clinic visit 1. The model was developed using stepwise backward selection by sequentially removing the covariate with the highest p-value. Fixed effects included treatment group and baseline temperature of the treatment leg. Potential covariates included demographics (age,

gender, race, employment, education), and clinical characteristics (body mass index, medications, co-morbidities, and taking pain medication). Only covariates with 0.05 level of significance remained in the model.

Data cleaning procedures

Data were analyzed for 304 subjects completing month 1 of the study (Figure 1). We report $N = 99$ ($n=53$ cooling; $n=46$ control) who returned study logs that were at least 85% accurate and contained no suspected fabrication (i.e., repeated patterns, different handwritings, or illogical temperatures or times). Twenty measurements outside the possible temperature range of (<22 and $>36^{\circ}\text{C}$) were removed.

Sample size

With a sample size of 46 subjects per group for longitudinal analysis [assuming 28 post baseline measurement time points, level of significance = 0.05 (two-tailed), correlation among repeated measures (intraclass correlation) no greater than 0.5], there was 85% power to detect a 0.45 standardized effect size between the groups.

Results

Demographic data

As seen in Table 1, there were no statistically significant differences between the treatment and control groups for mean age, gender, race, education, employment, body mass index (BMI), or medical conditions. Use of antianxiety or antidepressant medications (22% and 9%, $p=0.05$) and antihypertensive medications (76% and 58%, $p=0.04$) were statistically significantly different for cooling and control groups respectively.

The mean (SD) temperature at the baseline clinic visit across both groups for the treatment legs was 30.7°C (1.7°C), compared to initial home (log) temperatures of 32.4°C (1.6°C) (average of first three morning temperatures). For the month 1 return visit and the home temperature measurements prior to the visit (average of last three log morning temperatures), the mean (SD) temperatures were 31.6°C (1.6°C) and 32.2°C (1.7°C) respectively. In comparison of temperatures between groups (Table 2) no statistically significant differences were observed between the groups for either baseline ($p=0.82$) or month 1 ($p=0.30$).

Bland-Altman plots assessing agreement between clinic and home measurements showed that the bias between the two measurements was 1.8°C (95% limits of agreement: $-2.2 - 5.8$) with only 3 subjects falling outside the limits of agreement for baseline (Figure 2A) while agreement for the month 1 visit showed a bias of 0.6°C (95% limits of agreement: $-3.1 - 4.4$) with 4 subjects falling outside the limits of agreement (Figure 2B). As shown in the plots, subject home temperatures agree with clinic temperatures therefore, subsequent longitudinal analyses were conducted using subject home log temperatures.

In Figures 3, Spaghetti plots display temperatures obtained in the morning (A), before treatment (B), and after treatment (C) to assess for potential patterns over time for the treatment leg. Figure 3C shows a decrease in temperatures after cooling in the treatment

group as compared to the control group, providing evidence that both treatment groups adhered to the treatment protocol. The difference was not sustained until the morning measurement (Figure 3A).

Home temperatures over month 1 were analyzed for all 99 subjects for spline effects that would indicate stabilization point (i.e., a clear decrease or increase in temperature at a given time point during the 30 days) and, as shown in Figure 3A, no statistically significant decrease in skin temperature could be determined.

The multivariate analysis (Table 3) included 99 subjects' daily temperatures over one month and showed no statistically significant effect of the intervention on leg temperature ($p=0.12$). Temperatures were higher for subjects with hip or knee replacements ($p<0.0001$) or varicose veins ($p<0.0001$), than those without these medical conditions, controlling for all other covariates. However, temperatures were lower for subjects taking insulin ($p=0.0005$), diabetes pills ($p=0.015$), or medications for anxiety or depression ($p=0.0002$). Subjects with arthritis taking pain medication had lower temperatures than arthritic patients not taking pain medication ($p<0.0001$), controlling for all other covariates.

Discussion

Cooling chronically inflamed skin may offer protective benefits against ulcer development. We hypothesized that a 30 day intensive cooling regimen with a specially designed gel cuff would lower temperature by reducing inflammation, thus decreasing the risk for ulcer occurrence (new ulcer) or recurrence. This regimen did not result in a sustained lowered temperature nor was there a discernable sustained temperature reduction.

Several factors may play a role in the lack of temperature variability in response to cooling. Skin pathology associated with CVD is prevalent. The vasoregulatory capabilities of previously ulcerated and/or inflamed skin is impaired [17]. Consistent with others [18, 19], our previous studies have noted several pathophysiological functions of microcirculatory blood flow associated with venous disease. Under resting conditions, compared to unaffected skin on the contralateral limb of subject's with CVD, inflamed skin's perfusion is higher (14 perfusion units) [8]; perfusion pressure is increased (>10 mmHg) [20]; and, capillary refill time is rapid 20 per second (normal is 45 – 60 seconds) [21]. These results suggest that skin affected by venous “stasis or congestion” experiences abnormally faster movement of red blood cells in the capillaries which are under higher pressure, consistent with inflammation [11]. Cooling may not provide a long-term sustained effect due to lack of resolution of the underlying pathology.

The CVD population is generally older and experiences numerous co-morbid conditions. In our study, the average age was 61 years, and the most common co-morbid conditions were diabetes, hypertension, and obesity. Reduced microcirculation blood flow at rest is a well-known aging phenomenon due to endothelial cell damage [22] that impairs nitric oxide production needed for the synthesis of vasodilators [23]. As a consequence, a permanent state of vasoconstriction exists in the arteries, rendering blood flow inadequate to the rest of the vasculature in response to stress, especially cold [22].

Diabetes, hypertension and obesity cause alterations in skin blood flow, and in diabetes in particular, superficial skin microcirculation is significantly decreased after having diabetes for 10 years [24-28]. These pathologic microvascular changes associated with aging, diabetes, hypertension, and obesity may account for a lack of a statistically significant decrease in repeated local cooling cuff exposure on skin temperature. These changes may also explain why we did not find a definitive stabilization or sustained reduction in temperature in the treatment group.

Subjects having knee and hip surgery or varicose veins had higher skin temperatures. The presence of varicose veins is an early stage of venous disease, and surgical procedures of the legs and hips disrupt normal venous function and induce inflammation that can last for months. Venous thromboembolism is common after orthopedic procedures of the knees and hips, especially when varicose veins are present [29]. Varicose veins produce elevated skin temperature compared to normal skin [30-33].

The effects of medications taken for diabetes and pain medications for arthritis may have lowered skin temperature. The effects of specific diabetes medications on skin temperature are unknown, however, pain medications have marked thermoregulatory effects on body temperature [33]. Certain classes produce hypothermia but the relationship between body temperature, skin temperature of the legs and venous disease has not been elucidated. Certain medications may affect the central nervous system, leading to lower body temperatures, but whether the effects can be extended to the sympathetic system, mostly responsible for skin temperature regulation, is unknown.

Limitations

Skin temperature is affected by a host of internal endocrine and autonomic factors and environment conditions that could not be controlled under these non-controlled conditions, and may contribute to non-significant findings. Skin temperature is also affected by various disease states highly prevalent in this population, which was taking multiple medications, making temperature less reactive to cooling and the skin highly vulnerable to the potentially detrimental effects such as frostbite. Future studies should focus on dynamic changes in temperature such as cold stress recovery, which would allow for more precise temperature predictability in the presence of pathological conditions such as tissue inflammation.

Conclusions

Due in part to several possible factors including poor microcirculation, cooling did not result in persistently lowered temperatures after one month of treatment compared to placebo. Subjects may be better served by monitoring skin temperature on a daily basis, then cooling the skin in response to an elevation above baseline, rather than attempting to adhere to an intensive, prophylaxis, repetitive cooling regimen. A “prn” cooling approach when temperatures become elevated above baseline may provide a sufficient cooling milieu to prevent escalation of inflammation and thwart ulcer occurrence or recurrence. Ulcer prevention could result in fewer days lost from work, less use of pain medications, and improvements in quality of life. Health care providers would spend less time providing

lengthy and costly wound care and resources could be redirected to study new prevention mechanisms, all implications for a future clinical trial.

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Highlights

- There were no leg skin temperature differences between the two groups after the 1 month treatment
- The cooling cuff compared to placebo reduced temperature during cooling but this was not sustained
- Home temperatures did not show a clear “cut off” or sustained decrease during the 1 month treatment
- Hip/knee replacements, varicose veins and certain medicines resulted in temperature differences

Figure 1. CONSORT flow chart

Figure 2.

A. Bland-Altman plot of baseline clinic and patient log temperature agreement.

B. Bland-Altman plot of month 1 clinic and patient log temperature agreement.

A

B

Figure 3.

A. Morning temperature

B. Before treatment temperature

C. After treatment temperatures

Table 1

Demographics for month 1 patient log temperatures (N=99).

Variables	Cooling cuff n = 53 Mean ($\pm$ SD) %	Placebo cuff n = 46 Mean ($\pm$ SD) %	p value
Age	63.4 ($\pm$ 11.6)	59.5 ($\pm$ 10.8)	0.10
Gender			0.76
	Male 27 (50.9)%	22 (47.8)%	
	Female 26 (49.1)%	24 (52.2)%	
Race			0.28
	White 30 (56.6)%	21 (45.7)%	
	Black/African American 23 (43.4)%	25 (54.4)%	
Employment			0.50 ^A
Gainfully employed (full or part time)	14 (26.4) %	15 (32.6) %	
Volunteer, student, or home maker	3 (5.7) %	1 (2.2) %	
Unemployed	8 (15.1) %	9 (19.6) %	
Retired	28 (52.8) %	21 (45.7) %	
Education ^B			0.77
Less than high school	8 (22.9) %	8 (22.2) %	
High school graduate	18 (51.4) %	16 (44.4) %	
Some college	9 (25.7) %	12 (33.3) %	
Medical conditions			
Varicose veins	18 (28.6) %	14 (25.5) %	0.70
Blood clots	10 (15.9) %	10 (18.2) %	0.74
Hip and knee replacement	7 (11.1) %	5 (9.1) %	0.72
Diabetes	35 (55.6) %	31 (56.4) %	0.93
Hypertension	48 (76.2) %	37 (67.3) %	0.28
Arthritis	32 (50.8) %	21 (38.2) %	0.17
Thyroid problems	10 (16.9) %	6 (10.9) %	0.43
Medications			
Antianxiety or antidepressants	14 (22.2)%	5 (9.1) %	0.05
Insulin	19 (30.2) %	13 (23.6) %	0.43
Anticoagulants	16 (25.4) %	10 (18.2) %	0.35
Diuretics	14 (22.2) %	15 (27.3) %	0.53
NSAIDS	11 (17.5) %	7 (12.7) %	0.48
Diabetes pills	23 (36.5) %	21 (38.2) %	0.85
Pain pills	23 (33.0) %	14 (25.8) %	0.20
Cholesterol lower agents	33 (52.4) %	25 (45.6) %	0.45
Antihypertensives	48 (76.2) %	32 (58.2)v	0.04
BMI	37.7 ($\pm$ 10.2)	36.3 ($\pm$ 8.4)	0.44

Percentages may not sum to 100 due to rounding.

^A p value reported is for collapsed categories (Gainfully employed vs. Not gainfully employed) due to small cell size.^B Missing 28.

Table 2

Comparison of temperatures at baseline and month 1 clinic visit for treatment leg.

Variable	Cooling cuff N = 53	Placebo cuff N = 46	p value
N = 99	Mean (SD)	Mean (SD)	
Baseline temperature	30.7 (1.8)	30.8 (1.5)	0.82
Month 1 clinic visit temperature	31.7 (1.5)	31.4 (1.6)	0.30
Number of patient log days	27.3 (1.7)	27.8 (0.4)	0.08

Table 3

Multivariable analysis on month 1 patient log temperatures (N=99).

Variables	Parameter estimate	<i>p value</i>
Intervention		0.12
Control group	REFERENCE	
Treatment group	-0.148	
Day	-0.012	0.31
Intervention*Day		0.99
Control group	REFERENCE	
Treatment group	-0.0002	
Varicose veins	0.46	<.0001
Hip and knee replacement	0.63	<.0001
Arthritis	0.52	<.0001
Antianxiety or antidepressant meds	-0.50	0.0002
Insulin	-0.36	0.0005
Diabetes pills	-0.23	0.015
Pain	0.66	<.0001
Arthritis-by-pain	-2.07	<.0001