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ORIGINAL RESEARCH

The effect of a cryotherapy gel wrap on the microcirculation of skin affected by chronic venous disorders

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Abstract

Aim. The aim of this randomized clinical trial was to investigate a cryotherapy (cooling) gel wrap applied to lower leg skin affected by chronic venous disorders to determine whether therapeutic cooling improves skin microcirculation.

Background. Chronic venous disorders are under-recognized vascular health problems that result in severe skin damage and ulcerations of the lower legs. Impaired skin microcirculation contributes to venous leg ulcer development, thus new prevention therapies should address the microcirculation to prevent venous leg ulcers.

Methods. Sixty participants (n = 30 per group) were randomized to receive one of two daily 30-minute interventions for four weeks. The treatment group applied the cryotherapy gel wrap around the affected lower leg skin, or compression and elevated the legs on a special pillow each evening at bedtime. The standard care group wore compression and elevated the legs only. Laboratory pre- and post-measures included microcirculation measures of skin temperature with a thermistor, blood flow with a laser Doppler flowmeter, and venous refill time with a photoplethysmograph. Data were collected between 2008 2009 and analysed using descriptive statistics, paired t-tests or Wilcoxon signed ranks tests, logistic regression analyses, and mixed model analyses.

Results. Fifty-seven participants (treatment = 28; standard care = 29) completed the study. The mean age was 62 years, 70% female, 50% African American. In the final adjusted model, there was a statistically significant decrease in blood flow between the two groups ($-6.2[-11.8; -0.6]$, $P = 0.03$). No statistically significant differences were noted in temperature or venous refill time.

Conclusion. Study findings suggest that cryotherapy improves blood flow by slowing movement within the microcirculation and thus might potentially provide a therapeutic benefit to prevent leg ulcers.

Keywords: blood flow, chronic venous disorders, cryotherapy, nursing, randomized clinical trial, skin temperature, venous refill time

Introduction

Chronic venous disorders (CVDs) are under-recognized vascular health problems that result in severe skin damage and ulcerations of the lower legs, and restrictions on mobility. Affecting millions of individuals worldwide, and causing millions of lost workdays per year, CVDs are the most widespread of all vascular disorders and represent a full spectrum of abnormalities of the venous system including the microcirculation of the lower leg skin (Eklöf *et al.* 2004). In addition to enormous medical costs, the human costs are vast, producing pain and suffering and negatively affecting quality of life. Individuals with severe symptoms such as lipodermatosclerosis (skin thickening and hardening) have the highest prevalence of chronic skin ulcers (800 per 10,000 individuals) and the highest risk of venous leg ulcer (VLU) recurrence (Fowkes *et al.* 2001, Bryant & Nix 2007). Venous disorders account for 80–90% of all lower extremity ulcers, far exceeding the number of ulcers caused by arterial insufficiency and diabetes combined (O'Meara *et al.* 2010).

Background

Efficacious methods are needed that can reduce the negative outcomes of the disease, specifically, interventions to improve microcirculation and prevent VLUs in patients recalcitrant to guideline-guided standard care (compression, leg elevation, physical activities that pump the calf muscle) (Johnson & Paustian 2005). Cryotherapy has been established as an effective method to reduce tissue metabolism and improve microcirculation associated with acute inflammation and the study reported in this paper was undertaken to determine its efficacy on skin chronically inflamed by CVDs.

Theoretical framework

The preliminary phases of The Medical Research Council (MRC) framework were used to guide the development of this randomized exploratory clinical trial.

The MRC gives a series of systematic and sequential steps towards the development and evaluation of complex interventions to progress a body of knowledge to promote health (Craig *et al.* 2008). In the Preclinical phase, a steering team comprised of two researchers with expertise in cryotherapy, a physician who gives clinical care for patients with CVDs, and the principal investigator (PI) of this study, explored relevant theories and empirical evidence to determine the best choice of an intervention and to develop a strategic plan. The theoretical underpinning of this study was based on a pathophysiological model derived from an abundance of CVD literature which suggests that venous hypertension progresses to a severe inflammatory response in the skin manifesting in clinical stages, the most severe being ulceration, Stage 6 (Figure 1). Over time the skin inflammation becomes chronic, causing higher skin blood flow and skin temperature (Kelechi *et al.* 2003, Kelechi & Michel 2007). Functionally, impairment in the calf pump can also contribute to venous hypertension and alter venous refill time in the skin microcirculation. Skin temperature, blood flow and venous refill time were established as physiologic endpoints for this study.

Empirical evidence suggests that reduction in skin temperature and blood flow can be achieved with the application of cold (cryotherapy) to skin for short periods of time, generally no longer than 30 minutes, to produce hypothermia (Kanlayanaphotpom & Janwantanakul 2005). Ice, a well-known therapeutic treatment, applied to the skin causes an initial vasoconstriction of the skin blood vessels (Dykstra *et al.* 2009). The metabolic rate of tissue is reduced and the destruction of otherwise uninjured adjacent tissue is impeded by limiting injury (Chesterton *et al.* 2002, Merrick *et al.* 2003, Freiman & Bouganim 2005, Gach *et al.* 2005). Cryotherapy is particularly useful for reducing fluid leakage and bleeding, by reducing vessel permeability in the microcirculation (Schaser *et al.* 2007). This effect was considered to be important to address the pathophysiologic inflammatory processes that occur in CVD-affected skin.

The team further determined that preliminary pilot work previously conducted by the PI to evaluate the effects of cryotherapy on skin temperature and blood flow in a CVD-affected population were useful to inform phase 1 or the modelling phase. A small observational study of a commercially available cryotherapy gel wrap, placed around the lower legs of ten CVD-affected individuals (the area where CVD mainly affects the skin), was conducted to ascertain skin temperature and blood flow patterns during a 60-minute cooling period (Figure 2). Ice, the typical method for cooling skin is considered to be an overly aggressive form of cryotherapy for damaged skin. Gel, which does not freeze into a solid state, was considered to be safer and selected for this study.

The research question for skin temperature was: Will a cryotherapy gel wrap reduce leg temperature of CVD-affected skin, between 11 and 15°C below baseline, and sustain this reduction for at least 20 minutes? To reduce metabolic tissue activity, a reduction of 25°C below baseline is required for healthy individuals with acute musculoskeletal injuries. Thus, the target temperature was about half of this amount, considering that the CVD population has impaired skin microcirculation. Results indicate that skin temperature

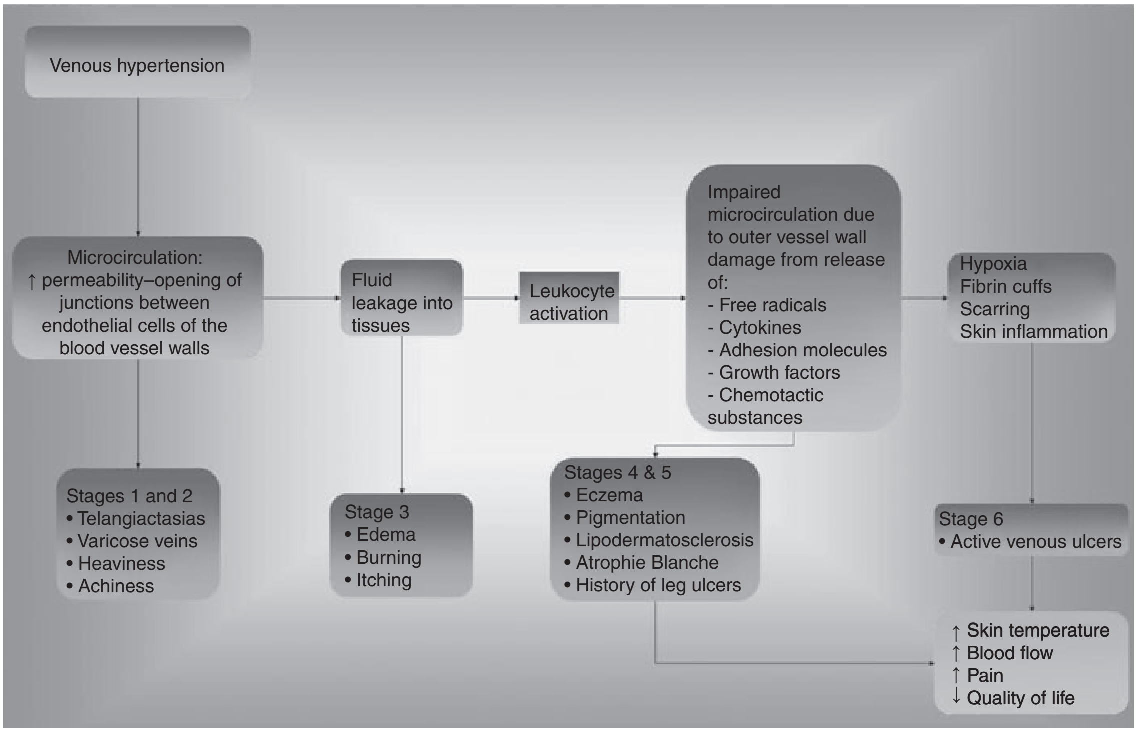

Figure 1 Schemata of microcirculation impairment of clinical states of chronic venous disorders.

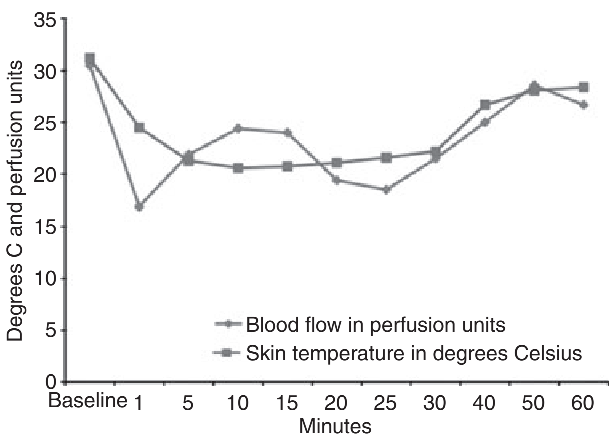

Figure 2 Blood flow and skin temperature during cryotherapy gel wrap study of ten volunteers with chronic venous disorders.

decreased at a constant, steady, safe and tolerable rate to approximately 11°C below baseline for 30 minutes, and then began to increase from 2 to 4°C every 10 minutes for the remaining 30 minutes.

The research question for blood flow was: Will a cryotherapy gel wrap decrease blood flow by 50% of its baseline for at least 20 minutes? Blood flow was found to follow a more variable pattern with a sudden decline, then a slight increase that could be attributed to a normal hyperaemic response, followed by a slight dip and then again a slow steady incline to 30 minutes. There was a more rapid blood flow increase for the remaining 30 minutes. The gel wrap was found to be tolerable to the subjects and was easy to apply.

Based on these findings and those of others (Mlynarczyk 1984), 30 minutes of cooling with a gel wrap resulted in the appropriate skin temperature and blood flow reductions. The study findings and practical details (e.g. identification of the easiest way to apply the wrap), informed the development of the outline of the cryotherapy procedure, which advanced planning of the intervention to the exploratory phase II of the MRC model. The steering team proposed a randomized clinical trial to study the effects of a cryotherapy gel wrap on blood flow and skin temperature in CVD-affected skin compared to a control group that received standard care only. The goal was to evaluate a 30-minute, daily dose for 1 month and compare findings to a sample of patients that did not receive the cryotherapy wrap. The once daily dosing was supported by research that suggests daily self-care management practices enhance therapeutic outcomes in populations with long term diseases [Chronic Disease Self Management Program (CDSMP) (http://www.ahrq.gov)]. In addition, the standard care model for preventing VLUs (Wound Ostomy Continence Nurses Society 2005) requires the daily use of compression stockings and leg elevation. These systematic and sequential activities aligned with the initial phases of the MRC model, and progressed to the conduct of a clinical trial, reported herein.

The study

Aim

The aim of this randomized clinical trial was to study patients with Clinical-Etiology-Anatomical-Pathological (CEAP) Classification Stages C4 (skin damage) and C5 (history of venous leg ulcers) (Eklof *et al.* 2004) to test the hypothesis that: patients randomized to the experimental treatment (cryotherapy gel wrap, compression stockings, leg elevation) compared to the standard care control treatment (compression stockings and leg elevation) will experience greater reduction in skin temperature and blood flow, and increased venous refill time (primary outcomes measures). The development of new venous ulcers during the course of the study was also tracked.

Design/methodology

Participants

A randomized clinical trial was conducted in 2008–2009 in South Carolina (USA), where there is a large proportion of racially and ethnically diverse individuals, and a high prevalence of vascular disorders. Data were collected at two sites, one in a rural wound clinic and the other at a research support centre in an academic medical centre. Eligibility criteria are reported in Table 1.

Sample size

Consistent with the purpose of a pilot study, the current study was not designed to confirm or refute hypotheses about treatment effectiveness (with corresponding emphasis on establishment of sufficient power for hypothesis testing); rather, its primary purpose was to obtain *preliminary* indicators of treatment effectiveness as indicated by effect sizes that suggest clinical relevance and trends towards statistical significance for treatment group comparisons. This information represents necessary input for the design of future, definitive, randomized effectiveness studies.

Therefore, sample size justification focused on precision of estimates of effect sizes rather than power of statistical tests. Primary effect sizes of interest are difference in change from baseline measurements between cryotherapy and control for skin temperature and blood flow. For a sample size of 28 patients per group, 95% confidence intervals (CIs) of these effect sizes had precisions of 0·67 and 4·67 corresponding to observed standard deviations of change scores of 1·8 and 12·6, respectively. The preliminary hypothesis tests of a *between* group pre to post treatment change had approximately 80% power to detect an effect size (change score) of 0·8 SD units (based on a two-sided pooled *t*-test comparison with level of significance $\alpha = 0{\cdot}05$).

Randomization

Patients were referred from wound clinics and primary care practices, or self referred by learning about the study from posted flyers, mailings, or word of mouth. Eligible patients were randomized into the treatment (1) or control group (2) by the study nurse using a computer-generated random

Table 1 Eligibility criteria

Inclusion	Exclusion
• aged 21 years and older • skin changes consistent with CEAP Stages C4 (pigmentation, eczema, lipodermatosclerosis, atrophy blanche) C5 (healed venous ulcer) • ankle-brachial index (ABI) of 0·80–1·3 mmHg • intact skin sensation measured with a 10 g monofilament • intact thermal sensation measured with thermal sensor tester TipTherm® • venous refill time (VRT) ≤25 seconds (indicates chronic venous insufficiency) measured with a venous photophlethysmograph (PPG) • agree to obtain or wear compression stockings for 2 weeks prior to the start of the study and during waking hours while enrolled • able to measure skin temperature with a dermal thermometer and record on provided log sheet	• open ulcers (cooling effects on open tissue unknown) • ABI <0·80 or >1·3 mmHg (indicates arterial insufficiency and cooling could further compromise blood flow leading to tissue necrosis) • decreased skin and thermal sensation (could result in a thermal injury from lack of sensation) • VRT >25 seconds (indicates normal refill time or lack of venous reflux and insufficiency) • unable to obtain or wear compression stockings for 2 weeks prior to the start of the study and during waking hours while enrolled • unable to measure skin temperature with a dermal thermometer or unable to record it on given log sheet

allocation sequence of a list of numbers (e.g. 1,1,2,1,2,2,1,2,2,1,1,1,2,2) indicating the sequence into which group the patient would be assigned. This list was given by the study biostatistician.

Interventions

After participants signed the informed consent, they were assessed for eligibility by the study nurse. If deemed eligible, participants were enrolled by the same study nurse, who collected all baseline data and gave all verbal and written study instructions. A DVD of the instructions with procedure demonstration was developed and tested prior to study implementation. The purpose of the DVDs was to standardize how instructions were delivered. Literacy was a major consideration, recognizing that some participants had lower literacy levels. After viewing, participants were tested on their understanding by taking a short verbal quiz and giving return demonstrations on study procedures (i.e. taking the leg temperature with the infrared thermometer). A checklist was used by the study nurse to document proficiency.

Cryotherapy. The cryotherapy group (n = 30) received the cryotherapy gel wrap (Southwest Technologies, Kansas City, MO, USA) to place around the most affected lower leg between the malleoli and bottom of calf muscle (gaiter area) for 30 minutes each day for 4 weeks while elevating both legs on a 10-inch high leg elevation pillow (pillow given to participants). The wrap is flexible and accommodative to many shapes and sizes of lower legs and comes inserted into two Lycra nylon coverings, the outermost removable for washing. The gel wrap was kept in the freezer, so freezer thermometers were given to participants to make sure that the freezer temperature was kept around 0°C. If the freezer temperature was −2°C or lower immediately before the wrap was used, participants were instructed to readjust the freezer temperature and perform the intervention when the temperature increased to 0°C. As a final 'barrier' precaution to further prevent frostbite injury, a polyethylene sleeve was slid onto the lower leg over which the gel wrap was affixed with an attached Velcro strap.

Participants were instructed to remove the compression stockings prior to the treatment and were given a 30-minute timer to use to ensure the procedure was done for the specified amount of time. Participants measured their lower leg skin temperatures with an infrared thermometer (TempTouch; Diabetica Solutions, San Antonio, TX, USA) prior to (baseline) applying the wrap, then immediately after to make sure the skin temperature did not drop lower than the target 10–15°C below the baseline. They also recorded skin temperature 12 hours later. This allowed investigators to determine if there was a sustained cooling effect. A temperature log sheet, clipboard and attached pen were given for this documentation. Participants were trained to use this standardized study log to record dates and times of treatment application, problems with the procedures, unusual symptoms experienced during the treatment and to document suggestions for protocol improvements. Weekly phone calls were made by the study nurse to evaluate fidelity and to problem-solve participant concerns.

Leg elevation. The control group (n = 30) received all study-related materials (leg elevator pillow, thermometer, logs) and received instruction through the DVD supplemented with verbal and written instruction. They elevated their legs for 30 minutes without wearing the compression stockings, recorded temperatures before and after elevation, and then 12 hours later. They wore compression stockings during waking hours. The same study nurse did all instruction and data collection for the control group.

Blinding. The study nurse and the participants were not blinded to treatment, however, the PI and Co-PI were blinded. The same study nurse collected both baseline and outcomes data due to budgetary constraints and the feasible nature of the study.

Data collection

The primary outcome variables for the study included physical measurements of skin microcirculation including blood flow, skin temperature and venous refill time. Data were collected during two visits, one prior to and one after the 4-week intervention. Blood flow (BF_{LD}), defined as the movement of blood in a defined area of skin, was measured with a laser Doppler flowmeter probe placed on the affected skin and recorded in perfusion units (PU). Skin temperature (T_{sk}), defined as energy conducted from the surface of the skin, was measured with a thermistor probe placed over the affected skin and recorded in °C (both Perimed, North Royalton, OH, USA). Venous refill time (VRT_{PPG}), defined as the time it takes blood to refill the microcirculation after a series of foot dorsiflexions (toes lift up off floor) that cause the calf muscle to contract and empty the veins, was measured with a probe placed above the medial malleolus and recorded in seconds with a photoplethysmograph (PPG) (Huntleigh, Eatontown, NJ, USA). A refill time ≥20 seconds suggests normal venous filling. A rapid refill time <20 seconds indicates that the calf pump was ineffective in ejecting blood and thus, the engorged larger vessels quickly refill the smaller vessels, an abnormal finding (Eberhardt & Raffetto 2005).

During visit one, interview data were obtained including demographic information such as age, gender, race/ethnicity, body mass index (BMI), leg circumference and history data such as smoking, previous ulceration, leg surgery or injury, co-morbid conditions, medications and type of lower leg compression and rural/urban status, number of adults in household and marital status. The primary outcomes variables were measured. During visit two, participants were asked about any changes in history data and then had the leg circumference and BMI measured, and skin temperature, blood flow and venous refill time. An end-of-study de-briefing survey was also completed to gain detail about participants' ratings of acceptability of the treatment, fidelity to protocol, and satisfaction with procedures.

Trial governance processes included oversight by a data and safety monitoring board (DSMB) that reviewed documentation of study procedures, evaluated participant logs to ensure safety of the cooling intervention, and met with the PI to discuss potential adverse events as the study progressed. However, there were no adverse events in this study. The PI and study nurse met at least weekly to discuss any problems related to fidelity, record keeping, or participant concerns. Participant tracking logs were maintained to monitor study processes including identification, screening, consenting and attrition. On a final log, the PI tracked study nurse fidelity to the protocol during the consenting, screening and enrolment processes.

Ethical considerations

The study was approved by the university and hospital institutional review boards where the study was conducted.

Data analysis

The data obtained by this study were analysed using Statistical Analysis Software SAS 9.1 (SAS Institute Inc., Cary, NC, USA). Unadjusted posttreatment means and mean change from baseline for the three primary outcome microcirculation measures skin temperature (T_{sk}), blood flow measured by laser Doppler (BF_{LD}) and venous refill time (VRT_{PPG}) were estimated using 95% CIs. Change from baseline scores for each outcome variable was compared for the cryotherapy and standard care conditions using pooled *t*-tests for this in subject design. Least squares adjusted mean change scores from baseline to follow-up for the outcome measures T_{sk}, BF_{LD} and VRT_{PPG} were compared in the two treatment groups and between the groups using a general linear model approach. Modelling occurred in a sequential fashion individually for the three outcome variables including sets of covariables such as demographic covariables age, race/ethnicity, gender, job category, area of residence and the clinical covariables BMI, ankle and calf circumference and wearing compression stockings (yes/no) as described by Cohen *et al.* (2003). Because qualitative conclusions were consistent across all models for each of the outcome variables, only the fully adjusted models are presented. Reported CIs are based on an approximate *t*-distribution. For all statistical tests, a value of $P < 0{\cdot}05$ was considered as statistically significant.

Results

Participant flow

Of the 60 individuals randomized into the two groups, 57 completed the study (Figure 3).

There were no protocol deviations from the study. Participants were recruited into the study starting January 2008 and the last participant completed the study in February 2009. Demographic and clinical characteristics at baseline appear in Table 2.

There were no statistically significant differences between cryotherapy and standard care groups with respect to demographic and clinical characteristics, except for ankle circumference. The majority of participants were aged 50–69 years, women, obese/morbidly obese, and reported wearing compression stockings. The groups were diverse with respect to race (White or African-American/Black) and occupation. As reported in Figure 3, two participants withdrew from the cryotherapy group ($n = 28$). One developed a blood clot in the non-cooled leg and the other experienced a family emergency. One participant withdrew from the standard care group ($n = 29$) due to developing a leg ulcer at week three from trauma.

Table 3 gives unadjusted means at baseline and follow-up and mean change from baseline with 95% CIs of the three primary outcome variables, BF_{LD}, T_{sk} and VRT_{PPG}, Unadjusted means are presented here as an overview of the raw data. Though means and 95% CIs are very similar at baseline for BF_{LD} for the cryotherapy and standard care groups, BF decreased from baseline in the cryotherapy group by 3·8 PU (95% CI [−0·6; 8·2]) but only slightly in the standard care group by <0·1 PU (95% CI [−6·6; 6·8]. The difference in change scores between the two groups ranged from −4·0 to 11·3 PU with 95% confidence ($P = 0{\cdot}33$). A slight increase in T_{sk} from baseline to follow-up was observed for both groups. The difference in change scores between the cryotherapy and standard care groups ranged from −1·0 to 0·9°C with 95% confidence ($P = 0{\cdot}77$).

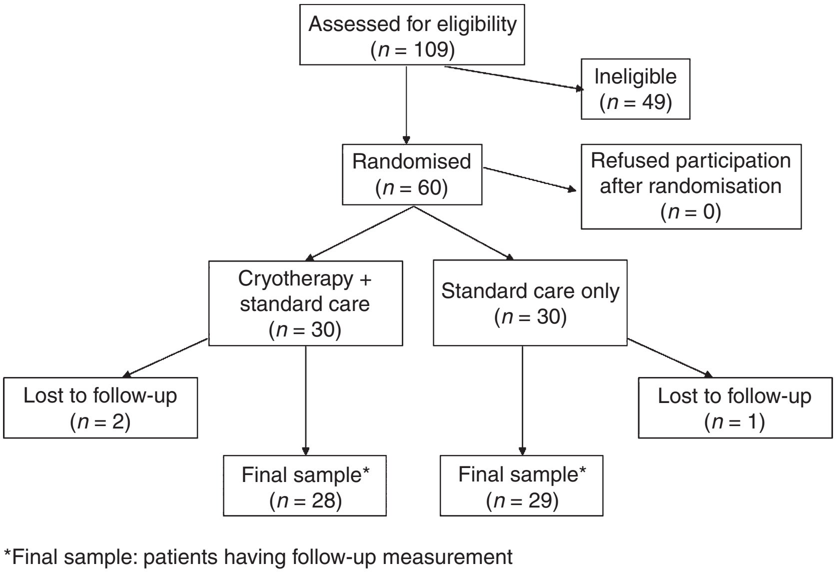

Figure 3 Enrolment tree.

The VRT_{PPG} for the cryotherapy group decreased a maximum of 5·7 seconds with 95% confidence. Difference in changes in VRT_{PPG} from baseline to follow-up is estimated with 95% confidence to range from 0·2 to 5·7. For the standard care group VRT_{PPG} is estimated (95% confidence) to decrease a maximum of 5·9 seconds. Differences ranged from −3·0 to 5·9. The difference in change scores between the two groups ranged from −3·5 to 6·6 seconds with 95% confidence (P = 0·55). With respect to leg ulcers, only one participant in the standard care group developed a new ulcer during the study period. A traumatic injury sustained during week 3 forced the withdrawal. The ulcer was unrelated to the treatment. Adjusted means for covariables are reported in Table 4.

For blood flow, values below 5 were set to missing because the skin was considered to be hypoxic and therefore the values would represent artificially low readings. BF_{LD} was consistently lower in the cryotherapy group compared to the standard care group (95% CI [3·6; 17·4 PU] vs. [8·2; 25·2 PU], P = 0·03). No statistically significant differences in adjusted means were observed for either T_{sk} or VRT_{PPG}. The 95% CI for the difference in T_{sk} ranged from −0·9 to 0·6°C (P = 0·627). Differences in VRT_{PPG} ranged from −4·6 to 5·3 seconds with 95% confidence (P = 0·890). In the full model 46% of the variation in BF_{LD} and T_{sk} could be explained by variation in the adjustment variables compared to 61% of the variation in VRT_{PPG}.

Due to the overweight and obese characteristics of the population, VRT_{PPG}, BF_{LD} and T_{sk} for three categories of BMI are reported in Table 5 as follows: underweight/normal <18·5 or 18·5–24·9; overweight 25·0–29·9 or obese 30·0–39·9; and morbidly obese >40. Cryotherapy had the greatest impact on VRT_{PPG} in the morbidly obese group and BF_{LD} in the overweight/obese, both approaching significance. Neither cryotherapy nor standard care significantly impacted skin temperature in any group (Table 5). There were no reported adverse events.

Discussion

Study limitations

Several study limitations are noted. The small sample sizes limit generalizations of the results. Various confounding factors may have distorted the true findings of the cooling effects. For example, the role of oedema as an insulator may have influenced that heat transfer from the skin. The gel wrap's less aggressive cooling nature may have extracted less heat, thus the impact on skin temperature was minimal. The several layers of barrier fabrics also could have impeded heat outflow from the skin. However, the impact of cooling on blood flow was positive but whether a sustained reduction in blood flow is therapeutic for preventing leg ulcers is unclear. To further our knowledge in this field, additional research to establish the effects of different types of cooling modalities when used as part of standard protocols that combine cold, elevation and compression for chronically inflamed skin would be useful. Similarly, testing of physiologic effects such

Table 2 Demographic and clinical characteristics at baseline ($N = 57$)

	Cryotherapy ($n = 28$)	Standard care ($n = 29$)	P value
Age, Mean (SD)	61·6 (12·1)	60·9 (13·4)	0·851
Age categories, % (frequency)			
35–49 years	17·9 (5)	17·2 (5)	0·993
50–69 years	53·6 (15)	55·2 (16)	
70 years or older	28·6 (8)	27·6 (8)	
Gender (Female)	71·4 (20)	69·0 (20)	0·839
Race/ethnicity			
White	46·4% (13)	48·3% (14)	0·992*
African-American/Black	50·0% (14)	51·7% (15)	
Latino	3·6% (1)	0	
Occupation			
Professional	42·9% (12)	44·8% (13)	0·562
Technical	32·1% (9)	20·7% (6)	
Labour	25·0% (7)	34·5% (10)	
Residence (Urban vs. rural)	78·6% (22)	79·3% (23)	0·946
Body mass index (BMI), Mean (SD)	36·8 (11·5)	39·3 (12·1)	0·439
BMI categories, % (frequency)			
Normal (18·5–24·9)	10·7 (3)	17·2 (5)	0·619†
Overweight (25·0–29·9)	21·4 (6)	10·3 (3)	
Obese (30·0–39·9)	32·1 (9)	24·1 (7)	
Morbidly obese (≥40·0)	35·7 (10)	48·3 (14)	
Calf circumference, Mean (SD)	42·5 (7·0)	44·0 (6·3)	0·419
Ankle circumference, Mean (SD)	24·9 (3·6)	27·3 (4·9)	0·035
Wore compression stockings (yes)	75·0% (21)	55·2% (16)	0·117
Previous leg ulcers, Mean (SD)	1·7 (3·9)	1·6 (2·8)	0·949
Arthritis, % (frequency)	53·6 (15)	55·2 (16)	0·903
Blood clots	32·1% (9)	24·1% (7)	0·501
Diabetes	25·0% (7)	44·8% (13)	0·117
Hypertension	53·6% (15)	69·0% (20)	0·233
Kidney problems	7·1% (2)	6·9% (2)	0·971
Poor arterial circulation	3·6% (1)	3·5% (1)	0·980
Hip replacement	10·7% (3)	17·2% (5)	0·478
Knee replacement	7·1% (2)	10·3% (3)	0·670
Thyroid problems	14·3% (4)	27·6% (8)	0·218
Varicose veins	53·6% (15)	34·5% (10)	0·147
Vein stripping	3·6% (1)	17·2% (5)	0·093

*From chi-squared test for White vs. African-American only.
†From chi-squared test for Normal or Overweight vs. Obese vs. Morbidly obese.

as reduced cutaneous oedema and inflammation would be advantageous. Finally, VRT as a measure of microcirculation is questionable.

To our knowledge, this randomized clinical trial was the first to determine the microcirculation effects of a short-term application of cryotherapy to lower leg skin in patients with CVDs classified by CEAP stages C4 and C5. These individuals are considered to be at the highest risk of developing leg ulcers. Baseline microcirculation measures of blood flow, temperature and venous refill time were compared after a 4-week, daily 30-minute cryotherapy gel wrap with standard care intervention or standard care alone. A statistically significant reduction in blood flow was achieved compared to baseline, supporting the hypothesis that blood flow would be decreased using cryotherapy. The mean blood flow in the cryotherapy group decreased from 14·6 to 10·8 PU compared to a very slight decrease from 15·5 to 15·27 PU in the standard care group during the study.

It is not known whether this reduction is clinically significant to prevent venous leg ulcers. There is limited knowledge about the effects of cryotherapy on superficial blood flow in chronically inflamed skin, however, data are available for healthy skin. Knobloch *et al.* (2006) reported that after a 30-minute application of a water-circulating

Table 3 Unadjusted means (SD) and [95% confidence intervals*] of the primary outcome variables comparing cryotherapy to standard care

	Cryotherapy	Standard care	Difference‡	*P* value
Venous refill time				
Baseline	18·1 (13·8)	12·7 (12·6)	5·5 (13·2)	0·126
	[12·8; 23·5]	[7·9; 17·5]	[−1·6; 12·5]	
Follow-up	15·1 (12·5)	12·2 (8·9)	3·0 (10·9)	0·315
	[12·1; 22·0]	[7·9; 15·4]	[−2·9; 9·0]	
Change from baseline†	3·0 (7·1)	1·4 (11·1)	1·5 (9·2)	0·553
	[0·2; 5·7]	[−3·0; 5·9]	[−3·5; 6·6]	
Blood flow				
Baseline	14·6 (9·7)	15·5 (9·5)	−0·90 (9·6)	0·748
	[10·5; 18·7]	[11·5; 19·5]	[−6·5; 4·7]	
Follow-Up	10·8 (5·3)	15·2 (10·8)	−4·4 (8·5)	0·078
	[8·6; 12·9]	[10·7; 19·6]	[−9·2; 0·4]	
Change from baseline†	3·8 (10·2)	−0·1 (14·7)	3·7 (12·6)	0·337
	[−0·6; 8·2]	[−6·6; 6·8]	[−4·0; 11·3]	
Skin temperature				
Baseline	30·5 (1·4)	30·5 (1·3)	−0·03 (1·4)	0·941
	[30·0; 31·1]	[30·0; 31·0]	[−0·8; 0·7]	
Follow-up	30·6 (1·3)	30·7 (1·6)	−0·14 (1·5)	0·718
	[30·0; 31·1]	[30·1; 31·3]	[−0·9; 0·6]	
Change from baseline*	−0·04 (2·0)	−0·04 (1·5)	−0·07 (1·8)	0·773
	[−0·8; 0·8]	[−0·5; 0·6]	[−1·0; 0·9]	

*Confidence intervals based on approximate *t*-distribution.
†Baseline minus follow-up: if difference > 0 then Baseline > Follow-up; if difference < 0 then Baseline < Follow-up.
‡Cryotherapy minus standard care: if difference > 0 then cryotherapy > standard care.

Table 4 Adjusted means [95% confidence intervals*] and r^2 from general linear models for primary outcome variables

Outcome	Cryotherapy	Standard care	Difference	*P* value	r^2
Skin temperature					
Final Model†	30·6 [29·6; 31·6]	30·8 [29·6; 31·9]	−0·2 [−0·9; 0·6]	0·627	0·46
Blood flow					
Final Model	10·5 [3·6; 17·4]	16·7 [8·2; 25·2]	−6·2 [−11·8; −0·6]	0·033	0·47
Venous refill time					
Final Model	11·5 [5·0; 17·9]	11·1 [3·7; 18·5]	0·3 [−4·6; 5·3]	0·890	0·61

*Confidence intervals based on approximate *t*-distribution.
†Model includes body mass index (BMI)-by-treatment, job category-by-treatment and residence area-by-treatment interaction terms.

cryotherapy device to the ankles of healthy volunteers, superficial microcirculatory blood flow measured at a 2-mm tissue depth was significantly reduced from 21 (SD 36) relative units (RU) at baseline to 7 (SD 5) RU ($P < 0·05$). In a later study of mid-portion Achilles tendon microcirculation in healthy volunteers, a combined cryotherapy/compression device applied continuously was compared to an intermittent device after three, 10-minute cryotherapy applications (Knobloch *et al.* 2008). Both cooling modalities significantly reduced superficial tendon blood flow. In the combined group, the change was from 43 (SD 46) arbitrary units (AU) to 10 (SD 19) AU and in the intermittent group, 42 (SD 46) AU vs. 12 (SD 10) AU, $P = 0·0001$. The blood flow results between the two devices after cooling were not significantly different.

In this study, the mean skin temperatures for the groups at baseline and after 4 weeks were unchanged [30·5°C (SD 1·4°C) vs. 30·6°C (SD 1·3°C); 30·5°C (SD 1·3°C) vs. 30·7°C (SD 1·6°C)]. Thus, the hypothesis that skin temperature would be decreased was not supported. A reduction in skin temperature was anticipated based on the assumption that if blood flow is reduced, skin temperature will also decrease. However, there are several issues such as room temperature, obesity, the gel material itself and the

Table 5 Venous refill time, blood flow, and skin temperature means (SD) and ranges [min; max] before and after treatment by body mass index (BMI) categories

BMI	Venous refill time							
	Cryotherapy				Standard care			
	Baseline	After	Difference	*P* value	Before	After	Difference	*P* value
< 18·5 or 18·5–24·9	(*n* = 3) 8·8 (3·8) [5·0; 12·7]	(*n* = 3) 7·2 (1·3) [5·7; 8·3]	1·6 (2·5) [0·7; 4·4]	0·562	(*n* = 5) 12·6 (8·9) [4·9; 27·7]	(*n* = 5) 12·1 (5·3) [7·7; 20·0]	0·5 (3·6) [−2·8; 7·7]	0·821
25·0–29·9 or 30·0–39·9	(*n* = 15) 10·4 (5·9) [2·8; 23·5]	(*n* = 15) 9·5 (4·2) [3·6; 17·7]	0·9 (1·7) [−0·8; 6·4]	0·736	(*n* = 10) 11·4 (9·8) [0·0; 35·0]	(*n* = 10) 8·1 (3·0) [4·4; 13·0]	3·2 (6·8) [−4·4; 22·0]	0·195
> 40	(*n* = 10) 18·5 (13·5) [3·0; 47·4]	(*n* = 10) 12·3 (7·1) [5·6; 30·7]	6·2 (6·4) [−2·6; 16·7]	0·081	(*n* = 14) 15·2 (10·4) [3·3; 31·1]	(*n* = 14) 18·2 (13·6) [4·5; 45·2]	−3·0 (−3·2) [−1·2; −14,1]	0·098

BMI	Blood flow							
	Baseline	After	Difference	*P* value	Baseline	After	Difference	*P* value
< 18·5 or 18·5–24·9	(*n* = 3) 19·9 (6·0) [15·0; 26·0]	(*n* = 3) 22·1 (10·1) [10·5; 29·0]	−2·2 (−4·1) [4·5; −3·0]	0·634	(*n* = 5) 16·4 (12·8) [8·0; 39·0]	(*n* = 5) 11·4 (2·7) [8·8; 14·0]	5·0 (10·1) [−0·08; 25·0]	0·043
25·0–29·9 or 30·0–39·9	(*n* = 15) 20·6 (16·1) [0·0; 46·0]	(*n* = 15) 15·7 (15·0) [0·0; 46·0]	4·9 (1·1) [0·0; 0·0]	0·051	(*n* = 10) 10·5 (8·8) [0·0; 24·0]	(*n* = 10) 13·5 (12·5) [2·0; 46·0]	−3·0 (−3·7) [−2·0; −22·0]	0·089
> 40	(*n* = 10) 14·5 (11·3) [7·0; 46·0]	(*n* = 10) 12·2 (7·9) [2·0; 30·0]	2·3 (3·4) [5·0; 16·0]	0·621	(*n* = 14) 12·8 (15·1) [0·0; 44·0]	(*n* = 11) 11·2 (7·0) [0·0; 27]	1·6 (8·0) [0·0; 17·0]	0·443

BMI	Skin temperature							
	Baseline	After	Difference	*P* value	Baseline	After	Difference	*P* value
< 18·5 or 18·5–24·9	(*n* = 3) 29·7 (0·36) [29·3; 30·0]	(*n* = 3) 28·8 (1·0) [28·0; 30·0]	1.1 (−0·64) [1·3; 0·0]	0·395	(*n* = 5) 29·2 (1·2) [28·9; 31·8]	(*n* = 5) 29·7 (0·5) [29·2; 30·5]	−0·5 (0·7) [−0·3; 1·3]	0·823
25·0–29·9 or 30·0–39·9	(*n* = 15) 30·0 (1·1) [28·8; 31·8]	(*n* = 15) 30·6 (1·1) [29·2; 32·6]	−0·6 (0·0) [−0·4; −0·8]	0·823	(*n* = 10) 30·6 (1·1) [29·6; 33·6]	(*n* = 10) 30·0 (1·3) [28·8; 33·3]	0·6 (0·2) [0·8; 0·3]	0·827
> 40	(*n* = 10) 31·4 (1·6) [29·1; 34·6]	(*n* = 10) 30·8 (1·3) [20·0; 32·3]	0·6 (0·3) [9·1; 2·3]	0·825	(*n* = 14) 30·6 (1·5) [26·9; 32·9]	(*n* = 14) 31·5 (1·5) [29·1; 33·5]	−0·9 (0·0) [−2·2; −0·6]	0·911

protective coverings placed over skin used to prevent thermal injury, that could explain the lack of skin temperature response.

It was anticipated that the initial mean skin temperatures would be higher. Previous studies demonstrate that CVD-affected skin is 1·8°C higher than skin temperature of individuals without CVDs [32·7°C (SD 1·8°C) vs. 31·2°C (SD 1·5°C); *P* = 0·004] (Kelechi *et al.* 2003, Kelechi & Michel 2007). The ambient temperature of the study examination room could not be controlled and therefore thermal neutrality was not achieved. In many cases, the air temperature was quite cool due to air conditioning and could have caused vasoconstriction. This could account for lower than anticipated skin temperature during the two visits.

The population of participants in this study was obese, defined as a BMI ≥30 kg/m^2. The mean BMI for the two groups were similar, 36·8 kg/m^2 (SD 11·5) and 39·3 (SD 12·1), respectively. Several individuals in the study were morbidly obese with a BMI ≥40 kg/m^2 (10/28 in the cryotherapy group; 14/29 in the standard care group). The ankle circumferences in the cryotherapy and standard care groups were 24·9 cm (SD 3·6) and 27·3 (SD 4·9), respectively. It was

What is already known about this topic

- Chronic venous disorders are under-recognized vascular conditions that can result in severe complications such as skin inflammation and ulcers.
- Non-pharmacologic therapies such as compression, elevation and exercise are the hallmarks of prevention for inflammation and ulcers.
- Cryotherapy, the application of cold temperatures to the skin, has been established as an effective non-pharmacologic method to reduce tissue metabolism and improve microcirculation associated with acute inflammation, but not for prevention of chronic inflammation and ulcers associated with chronic venous disorders.

What this paper adds

- Cryotherapy reduces blood flow (an indicator of microcirculation) after a 4-week, 30-minute application of a gel pack to the affected skin.
- Patient's tolerance of the cryotherapy intervention and feasibility of using the gel wrap were acceptable.

Implications for practice and/or policy

- Cryotherapy may be a breakthrough prevention intervention that gives long-term benefits including a reduction in skin inflammation and leg ulcers.
- Future clinical research on the use of cryotherapy, added to the standard of care, could give a new preventive care model for venous leg ulcers.

difficult to determine whether oedema associated with CVDs or thick adipose tissue from obesity accounted for the large ankle circumferences. Otte *et al.* (2002) found that thicker subcutaneous adipose tissue required much longer cooling times in healthy volunteers with differing subcutaneous adipose thicknesses. Standard cooling effect, defined as a 7°C decrease from baseline in intramuscular temperature measured at 1 cm sub adipose, was measured under crushed ice applied to the thigh. To achieve this effect, the thickest adipose tissue (31–44 mm) required 58·6 minutes of cooling compared to 8·0 minutes for adipose thickness of 0–1 mm. Therefore, the 30-minute application time in our study might not have been adequate to produce a therapeutic sustained cooling effect.

A second precautionary measure was the gel material itself. The gel was selected thinking it would be safer for cooling damaged skin than crushed ice, peas, or water immersion even though the former has been shown to cool less effectively (Kennet *et al.* 2007). Gel reduced skin temperature by 13·19 ± 5·07°C compared to 19·56 (3·78°C) with crushed ice, the most effective cooling modality. Kanlayanaphotpom and Janwantanakul (2005) found that gel produced a mean surface skin temperature of 13·9°F (4·1°C) in a study of 50 volunteers after a 20-minute cryotherapy application to the skin overlying the right quadriceps femoris muscle compared to an ice pack that reduced mean skin temperature to 10·2°F (3·5°C). Chesterton *et al.* (2002) also found that after 20 minutes of cooling the anterior thigh of 20 volunteers, gel did not cool skin sufficiently; 14·4°F (2·53°C) to induce localized skin analgesia, reduce nerve conduction velocity and reduce metabolic enzyme activity to clinically relevant levels compared to frozen peas; 10·8°F (2·28°C). Thus, gel was found to be a less aggressive or effective modality to offer therapeutic benefits in healthy volunteers in these studies. Although gel cools less effectively or aggressively, it does reduce skin temperature and reduces blood flow, a major abnormality associated with CVD.

A third precautionary measure that could have mitigated a cooling effect was the fabrics used to prevent thermal injury. A polyethylene sleeve was slid onto the leg, over which the gel wrap was placed. The gel was also encased in two coverings, the outer layer made of polyester. These multiple layers could have prevented a beneficial cooling effect. Shibuya *et al.* (2007) studied skin temperature under different bandage dressings over which three different water-circulating cryotherapy devices (boot and wraps) were applied to the mid-foot of healthy participants. For each dressing and cryotherapy device, skin temperature was measured every 15 minutes for a 180-minute cooling period. Over two layers of a compression bandage, no device significantly lowered the temperature from the mean readings of 33·4°C during the cooling period. Blood flow was not studied. It is thought that a skin temperature range between 20°C (68°F) and 30°C (86°F) is needed to attain oedema reduction. Therefore, fabrics can significantly alter cooling by preventing the transfer of heat from the skin surface thus negatively impacting therapeutic benefits.

The hypothesis that venous refill time (VRT) would improve (increase in seconds) was not supported. VRT decreased in the cryotherapy group by 3 seconds, from 18·1 to 15·1 seconds. Faster refill time is associated with impaired venous blood flow. VRT gives information about the overall function of the venous system and lacking among the studies of the therapeutic effects of surgery, compression therapy and exercise is cryotherapy (Beraldo *et al.* 2007). VRT may not have been an appropriate microcirculation measure because it is dependent on the efficiency of the calf muscle pump and an intact range of ankle motion. Oedema, obesity, arthritis and a history of blood clots in the lower legs can all affect the calf muscle pump and range of motion and were present in several individuals in this study. Thus, other methods to measure venous refill time should be considered in future studies as the handheld device used in this study produced questionable findings of accuracy and sensitivity.

Conclusion

The new knowledge gained from this study of a condition that chronically inflames the skin and holds promise for improvements in the existing standard of care to manage CVDs, and in particular, for individuals with CVDs that are not amenable to surgical or pharmacological interventions. While compression and leg elevation are the mainstay of treatment, many individuals are unable to or chose not to comply with this treatment, and may prefer, instead, to cool the skin with an easy to apply gel wrap. Cooling the skin was found to be practical and feasible and might give an alternative mechanism for managing CVDs. Worldwide, nurses are primarily responsible for caring for patients with CVDs and leg ulcers, and are vital to adding to practice changes by exploring new innovations to manage long-term illnesses such as CVD. A larger trial, currently underway, might give nurses an evidence-based treatment to add to the armamentarium of current venous ulcer prevention practices.

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Conflict of interest

No conflict of interest has been declared by the authors.

Author contributions

TK, MM and JZ were responsible for the study conception and design. TK did the data collection. MM did the data analysis. TK, MM and JZ were responsible for the drafting of the manuscript. DK made critical revisions to the paper for important intellectual content. MM gave statistical expertise. TK, MM and JZ obtained funding. DK supervised the study.

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